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This is the First Annual Report (months 1-12) for the Career Development Award (CDA) given Dr. Richard Day, Department of Biostatistics, University of Pittsburgh. This CDA was specifically intended to support Dr. Day in the development of a Health-Related Quality of Life Program (HRQL) for the National Surgical Adjuvant Breast and Bowel Project (NSABP). Important Achievements for Months 1-12 included: (a) completion of data collection and initial HRQL data analysis for the NSABP Breast Cancer Prevention Trial; (b) the design and implementation of HRQL studies for three new NSABP treatment trials and for one new NSABP prevention trial; (c) the implementation and debugging of enhanced data collection and processing methods (i.e., scannable forms) for one new treatment and one new prevention trial. Important Delays for Months 1-12 included design of HRQL components for the B-29 protocol and a breast cancer survivors study which was delayed as a consequence of the requirements of other priority tasks. Except for the work proposed for B-29 and the breast cancer survivors study, which will be addressed during months 13-24, all planned components of Dr. Day's original Statement of Work for his CDA are proceeding according to ahead of schedule.

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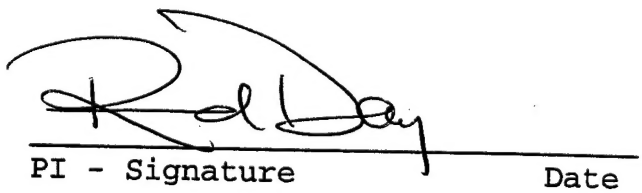

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Career Development Award:

Development of an Integrated Program of Health-Related Quality of Life Research for the National surgical Adjuvant Breast and Bowel Project

Richard Day, Ph.D.
Department of Biostatistics
University of Pittsburgh

First Annual Progress Report
September 1 1997 to September 30 1998

1. Introduction

This is the First Annual Report (months 1-12) for the Career Development Award (CDA) given Dr. Richard Day, Department of Biostatistics, University of Pittsburgh. This CDA was specifically intended to support Dr. Day in the development of a Health-Related Quality of Life Program (HRQL) for the National Surgical Adjuvant Breast and Bowel Project (NSABP). Specific aims proposed for the CDA included:

a. Analysis of HRQL data already collected in the NSABP Breast Cancer Prevention Trial (BCPT);

b. Refinement and extension of HRQL methods to analyze the data from new treatment studies;

c. Design and implementation of new HRQL components for planned NSABP treatment and prevention trials;

d. Testing and implementation of a computer-based scannable system for the design of HRQL forms and entry of data;

e. Enhancement of minority participation in NSABP trials and the implementation of measures focusing on HRQL-related issues in women of color.

Work completed over the first 12 months of Dr. Day's CDA will be summarized in terms of the planned schedule of Technical Objectives specified in the original application's Statement of Work. (pg.s 9-10).

2. Body

2.1 Technical Objective 1: BCPT Data Analysis

2.1.1 Task 1: Months 1-12: Evaluation of BCPT data sets with consultants and mentors and design of a detailed plan of analysis.

2.1.2 Progress to date: Progress on Task 1 during the first 12 months of the CDA has gone considerably beyond that scheduled in the original Statement of Work. The key event during in the NSAPB BCPT over the past 12 months was the recommendation by the data safety monitoring committee in March 1998 to unmask the trial and to publicly announce the findings. Following this decision, the primary tasks of the BCPT staff were to prepare initial communications summarizing the trial data and to present the critical findings of the BCPT in open scientific forums.

The health-related quality of life (HRQOL) data was considered a key aspect of the initial data requiring analysis and presentation. The proposed mentoring process and development of a plan of analysis outlined in Dr. Day's initial Statement of Work had to be accelerated. Three tasks were given priority:

a. Review of HRQL data for summary inclusion in the initial clinical communication from the BCPT.

b. Development of a HRQL data summary for presentation at the 19th Annual Meetings of the Society for Clinical Trials, Atlanta, GA, 17-20 May 1998.

c. Preparation of an initial HRQL communication for publication in the scientific literature immediately following the initial clinical communication.

All three of these tasks have been completed in the first 12 months of Dr. Day's CDA. The text of the initial clinical communication from the NSABP BCPT is included in the Appendix. Over and above the accelerated schedule, Dr. Day actually wrote and presented two scientific papers at the Society for Clinical Trials (SCT) Meeting. This was due to the fact that Dr. Joseph P. Costantino, who was scheduled to present one of the NSAPB papers, was required to present the BCPT clinical outcome data at the American Society of Clinical Oncologists (ASCO) Meeting which was occurring in Los Angeles on the same dates. The Appendix includes copies of the published abstracts and slides for the two papers written and given by Dr. Day at the 1998 SCT Meetings. Finally, Dr. Day will be the primary author on the initial HRQL communication from the NSABP BCPT. This initial communication is in the final stages of preparation for

submission to the Journal of the National Cancer Institute (JNCI). This paper was completed with the support of Dr. Day's key mentors and collaborators: Dr. Ganz, Weissfeld, and Dr. Cella. During this period, Dr. Day established an ongoing weekly seminar at the University of Pittsburgh to review and work on BCPT HRQL data. Interaction with mentors and other consultants outside of Pittsburgh was carried on through scheduled NSABP national meetings (Washington DC, June 1998), professional meetings (SCT May 1998) and consultant visits to Pittsburgh. The Appendix contains the current draft version of the initial HRQL communication from the NSABP BCPT and the published version of a paper in Statistics and Medicine with Dr. Ganz on participant compliance in the BCPT. It is expected that the draft HRQL paper will be submitted to JNCI by the second week in October 1998.

2.1.3 Plan of Work: Months 13-24: Once the initial NSABP HRQL communication has been published, the goal is to begin publication of a series of detailed methodological and clinical analyses of the BCPT HRQL data. Due to concerns expressed by the Federal Drug Administration (FDA) and its timeliness in the literature, the first paper in this series will be an in-depth look at the data on affective distress and depression and his the working title: Does tamoxifen cause depression?

2.2 Technical Objective 2: Analysis of Data from NSABP Treatment Trials

2.2.1 Task 1: Months 6-24: Collection of B-23, B-29 and breast cancer survivor data; plan of data analysis with consultants and mentors.

2.2.2 Progress to Date: A separate HRQL protocol (including the design of HRQL instruments) for the B-23 Study was written, as well as reviewed and approved by the National cancer Institute by April 1998 (see Appendix). The B-23 HRQL study was implemented in May 1998 with the objective of collecting a total of 240 subjects by the end of the trial. Data collection is currently in progress and 146 patients have been enrolled in this study.

Unexpected circumstances have delayed the initiation of work on the design and implementation of HRQL studies for the B-29 and breast cancer survivor study. Over the past 12 months, Dr. Day's attention has been directed to the development of HRQL components for three alternative, high-priority NSABP studies:

a. **Study of Tamoxifen and Raloxifene (STAR)** – STAR is the second large-scale, multicentric prevention trial to be carried out by NSABP. The time table for the development of the P-2 protocol was moved forward in time due to the unexpected closing of the P-1 (BCPT) protocol in March 1998 by the Data Safety monitoring Committee. This meant that Dr. Day had to give immediate attention to the assessment

of the P-1 HRQL results in terms of their implications for the design of the new prevention protocol (P-2). As currently envisioned, STAR will involve the recruitment of 22,000 women at high risk for breast cancer who will be randomized to two treatment arms: one receiving tamoxifen and the other raloxifene. HRQL will be assessed in a sub-sample of at least 3,000 participants. Together with Dr. Patricia Ganz, Dr. Day was responsible for selecting a P-2 HRQL committee and developing the rationale for the battery of scannable HRQL instruments to be used in the P-2 protocol, along with the associated sample size estimates and a proposed plan of implementation. It is planned that STAR be implemented before the end of 1998, which has involved Dr. Day is an ongoing process of HRQL instrument design and development.

b. **B-30 Protocol** – This is a 3 arm randomized trial comparing adjuvant adriamycin and cyclophosphamide followed by taxotere (Arm 1:AC-T) to adreiamycin and taxotere alone (Arm 2:AT) and adreiamycin, cyclophosphamide, and taxotere together (Arm 3:ACT) in patients with positive axillary lymph nodes (see Appendix). This protocol was given high priority by the NSABP Clinical Operations Center and Dr. Day was asked to help develop a HRQL component for this study. Dr. Day was central in the design of two separate HRQL components for the B-30 protocol. The first component represents a general HRQL assessment in the 3 arms and uses the following instruments: Functional Assessment of Cancer Therapy Questionnaire – Breast (FACT-B), the Medical Outcomes Study Vitality Scale from the Short Form-36 (SF-36), a treatment-specific symptom checklist (SCL), and a NSABP HRQL rating scale. The second component involves a study of the effects of chemotherapeutic alkylating agents on menstrual functioning. Dr. Day, together with Dr. Ganz, developed a menstrual history questionnaire designed to track the incidence of amenorrhea in eligible B-30 participants and investigate its relationship to HRQL measures and disease-free survival (DFS). Dr. Day also had responsibility for developing a plan of statistical analysis for both HRQL components and associated sample size estimates. As the present time, this protocol is under review by NCI and Dr. Day will have responsibility for drafting a reply to any HRQL questions. It is planned that this protocol will open by November 1998 (see Appendix).

c. **C-06 Protocol** – This is a two arm trial comparing oral uracil/ftorafur (UFT) plus leucovorin (LV) with 5-fluorouracil (5-FU) plus LV in the treatment of patients with stages II and III carcinoma of the colon. Although this is a colon cancer, rather than a breast cancer trial, it was given high priority as a vehicle for testing scannable HRQL forms and as a potential model for future breast cancer studies. The work related to this protocol was very time intensive and included the development of a research protocol and plan for statistical analysis; the design of a

complex scannable instrument battery and translations to French and Spanish; implementation and monitoring of the HRQL component of the study. The results of this work will be further discussed under Technical Objective 4.

As noted above, work on these 3 high-priority NSABP protocols has delayed the implementation of HRQL work on B-29 and a breast survivor study. However, this is simply deferred work. As soon as P-2 and B-30 have been implemented, ideally by the end of the year, Dr. Day will be able to return to the proposed plan of work. It may be possible, to in fact develop and implement the delayed studies in a very efficient manner which minimizes lost time in the second 12 months of the CDA.

2.2.3 Plan of Work: Months 13-24: The first priority for months 13-24 is the implementation of the P-2 and B-30 protocols. The second priority is the development of an HRQL component and the implementation of the B-29 and a proposed breast cancer survivor studies.

2.3 Technical Objective 3: Trial Design and Development of an Instrument Battery

2.3.1.a Task 1: Months 1-9: Design and implement B-29 and long-term breast cancer survivor study.

2.3.1.b Task 2: Months 9-36: Complete evaluation of scales for instrument battery and convert into scannable modular form.

2.3.2.a Progress to Date on Task 1: The selection of research protocols that require immediate attention is an organizational decision by the NSABP leadership. As noted above, work on B-29 and the breast cancer survivor study has been delayed. Dr. Day's time has instead been focused on the design and implementation of HRQL components for three other high-priority protocols (i.e., P-2, B-30 and C-06) requiring immediate Headquarters attention.

2.3.2.b Progress to Date on Task 2: Significant progress has been made over the past 12 months on the development of a standard modular instrument package for NSABP HRQL studies. Data collection experience in the B-23, C-06 and P-1 studies, as well as in the design of the B-30 and P-2 protocols has allowed us to identify and begin to evaluate a series of HQRL instruments that may be converted to a modular scannable form. These instruments include:

a. **Medical Outcomes Study Short Form 36 (MOS-SF 36)** – The SF-36 includes 8 specific subscales (i.e., physical functioning, role functioning-physical, bodily pain, social functioning, mental health, role

functioning-emotional, vitality, general health perceptions, change in health) that may be "modularized" in order to draw upon certain domains of HRQL functioning. For example, the general health perceptions and change in health scales were used modularly in B-23, the vitality scale is used modularly in the B-30 and B-23 trials, and the mental health scales are used modularly in the P-1 and B-30 trials.

b. **Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) Questionnaire** – The FACT-B has a series of potentially modular subscales (i.e., physical well-being, social/family well-being, relationship to doctor, emotional well-being, functional well-being, additional breast cancer-specific concerns). Although, to date, we have always implemented the FACT-B as a unitary instrument (B-23, B-30), it is becoming increasingly clear that such extensive forms need to be far more targeted to specific hypotheses in treatment trials. Like the SF-36, the subscales in the FACT have been independently validated, and may be used in future protocols in a modular form. We are currently undertaking discussions with Dr. Cella, the author of the FACT, designed to develop a strategy for the selection of modular components of the FACT that has minimal effect on the comparative validity of the resulting data.

c. **Protocol-Specific Symptom Check-Lists** – As we develop new protocols, we are developing a pool of specific items from which to choose in the creation of treatment-specific symptom check lists. Data collection in the B-23, P-1 and C-06 studies have permitted us to gain valuable experience with different types of symptom rating systems (e.g., yes/no vs. 4 or 5 level Likert scales) and with applicability of different symptom formulations. With the completion of B-23 and C-06, it should be possible to quantitatively formalize this experience.

2.3.3 Plan of Work: Months 13-24: With regard to Task 1, the goal for months 12-24 is to return to the planned program of work on B-29 and a breast cancer survivor study. With regard to Task 2, the goal is to continue working on the modularization of key HRQL instruments with their authors. It is becoming clear based on the early NSABP HRQL studies (B-23, P-1, C-06) that we must use shorter questionnaires. This means the increasing use of individual, targeted scales (e.g., SF 36 vitality or mental heath scales) from larger instruments in order to test more specific HRQL hypotheses without violating important psychometric properties of the parent instruments. With the impending completion of the data collection on these early HRQL protocols, we should have the data to quantitatively assess these issues.

2.4 Technical Objective 4: Enhanced Data Collection and Processing Methods

2.4.1.a Task 1: Months 1-9: Implementation of computerized system for scannable HRQL forms.

2.4.1.b Task 2: Months 9-24: Pilot testing and debugging the processing of scannable forms in ongoing studies.

2.4.2 Progress to Date: Progress on this objective is well ahead of the projected schedule in the original Statement of Work. Following consultations with NSABP staff, it was decided that the C-06 study was the best protocol in which to implement scannable HRQL forms (see Appendix). The reasons for this decision included the fact that C-06 would accrue a substantial number of HRQL subjects (n=988) and that recruitment would occur relatively quickly. Pilot testing and debugging of the scanning software proceeded relatively smoothly and was completed within six months of the opening of the trial and a report was submitted to Dr. Samuel Wieand, Director of the Biostatistical Center (see Appendix). To date, a total of 990 subjects have been processed in the C-06 study representing approximately 2500 HRQL forms. At the current time, a system-wide review is being undertaken to document the strengths and weaknesses of the scanning system. This system review will eventually lead to decision about the extent to which the scannable system will be implemented in forthcoming treatment trials. With regard to new STAR prevention trial (P-2), a decision has already been made to implement scannable forms as part of the HRQL component based on the experience achieved in the P-1 trial. Development and debugging of the scannable forms for the P-2 study is scheduled before the beginning of the year.

2.4.3 Plan of Work: Months 13-24: Development and debugging of the scannable forms for the P-2 study is scheduled before the beginning of the year. Completion of the system-wide review on the treatment side will be completed shortly and will determine the extent to which scannable HRQL forms will be implemented in forthcoming NSABP treatment protocols.

2.5 Technical Objective 5: Minority and Diversity Issues

2.5.1 Task 1: Months 1-18: Develop evaluation plan for prevention trial minority recruitment program; complete manuscript for review of BCPT minority recruitment experience; recruit African American or Hispanic scholar for HRQL expert committee.

2.5.2 Progress to Date: Issues surrounding minority recruitment are very sensitive, particularly within a prevention context. At the present time, a Quality of Life consultation is being planned which will take place at NSABP Headquarters prior to the end of 1998. This consultation will include NSABP Headquarters and Biostatistical staff concerned with HRQL-related issues and a selected group of scholars and scientists from NSABP collaborating centers and outside HRQL specialists. The goal of this consultation is to review the current and future role of HRQL research in NSABP prevention and treatment trials and to produce a series of recommendations for action by the NSABP leadership. A significant part of the issues to be discussed at this consultation will be the membership of the Quality of Life Expert Committees for the Treatment and Prevention Trials and the identification of minority members for both committees. Over the past 12 months, Dr. Day has developed a familiarity with minority members currently involved in NSABP trials, particularly through the process of completing Spanish language translations of the instruments used in B-23, C-06 and B-30. As part of this consultation, it should be possible to select both an African American and a Hispanic scholar to sit on the HRQL expert committees. The NSABP leadership has also expressed interest in the completion of a manuscript reviewing the experience of the group in minority recruitment in the BCPT (P-1). This manuscript will help to develop policy for implementation in P-2 and can be initiated after the first wave of clinical manuscripts have been published for P-1.

2.5.3 Plan of Work: Months 13-24: Dr. Day will be directly involved in completing all of the following tasks by the early part of 1999:

a. A strategy paper will be available which provides an overview of future HRQL-related goals for NSABP treatment and prevention trials;
b. New HRQL Expert Committees will be constituted for NSABP treatment and prevention trials, including minority population representatives; and,
c. A manuscript will be completed analyzing the minority recruitment experience in the P-1 protocol and reviewing plans for improved minority recruitment in P-2 study.

3. Conclusion

3.1 Summary of Important Achievements for Months 1-12:

a. Completion of data collection and initial HRQL data analysis for the NSABP Breast Cancer Prevention Trial (protocol P-1); presentation of BCPT HRQL results at scientific meetings and drafting of initial communication for Journal of the National Cancer Institute; publication of paper on BCPT participant compliance in Statistics in Medicine.

b. Design and implementation of HRQL studies for three new NSABP treatment trials (B-23, C-06, B-30) and for one new NSABP prevention trial (STAR, P-2).

c. Planning, implementation and debugging of enhanced data collection and processing methods (i.e., scannable forms) for one new treatment (C-06) and one new prevention trial (STAR, P-2).

d. Development of an initial components of a battery of scannable, modularized instruments (SF-36, FACT-B, SCL) for use with future NSABP treatment and prevention trials.

e. Planning an organization of a NSAPB Headquarters meeting for the purpose of reviewing the membership of the HRQL Treatment and Prevention Expert Committees and producing a set of recommendations to guide future NSABP HQRL activities based on the experience of the last 12 months.

3.2 Summary of Important Delays for Months 1-12:

a. Design of HRQL components for the B-29 protocol and a breast cancer survivors study has been delayed as a consequence of the requirements to other priority tasks.

3.3 Comment:

Except for the work proposed for B-29 and the breast cancer survivors study, which will be addressed during months 13-24, all planned components of Dr. Day's original Statement of Work for his CDA are proceeding according to ahead of schedule.

APPENDIX

a. P-1 Initial Communication

Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study

Bernard Fisher, Joseph P. Costantino, D. Lawrence Wickerham, Carol K. Redmond, Maureen Kavanah, Walter M. Cronin, Victor Vogel, André Robidoux, Nikolay Dimitrov, James Atkins, Mary Daly, Samuel Wieand, Elizabeth Tan-Chiu, Leslie Ford, Norman Wolmark, and other National Surgical Adjuvant Breast and Bowel Project Investigators

Background: **The finding of a decrease in contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy led to the concept that the drug might play a role in breast cancer prevention. To test this hypothesis, the National Surgical Adjuvant Breast and Bowel Project initiated the Breast Cancer Prevention Trial (P-1) in 1992.** ***Methods:*** **Women (N = 13388) at increased risk for breast cancer because they 1) were 60 years of age or older, 2) were 35–59 years of age with a 5-year predicted risk for breast cancer of at least 1.66%, or 3) had a history of lobular carcinoma *in situ* were randomly assigned to receive placebo (n = 6707) or 20 mg/day tamoxifen (n = 6681) for 5 years. Gail's algorithm, based on a multivariate logistic regression model using combinations of risk factors, was used to estimate the probability (risk) of occurrence of breast cancer over time.** ***Results:*** **Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided *P*<.00001), with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50–59 years (51%), and 60 years or older (55%); risk was also reduced in women with a history of lobular carcinoma *in situ* (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50% (two-sided *P*<.002). Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease; however, a reduction in hip, radius (Colles'), and spine fractures was observed. The rate of endometrial cancer was increased in the tamoxifen group (risk ratio = 2.53; 95% confidence interval = 1.35–4.97); this increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group. The rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older.** ***Conclusions:*** **Tamoxifen decreases the incidence of invasive and noninvasive breast cancer. Despite side effects resulting from administration of tamoxifen, its use as a breast cancer preventive agent is appropriate in many women at increased risk for the disease. [J Natl Cancer Inst 1998;90:1371–88]**

On June 1, 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented a randomized clinical trial to evaluate the worth of tamoxifen for the prevention of breast cancer in women considered to be at increased risk for the disease. (The term "prevention," as used in this article, indicates a reduction in the incidence [risk] of invasive breast cancer over the period of the study. Although tamoxifen prevented the appearance of a substantial number of breast cancers over the duration of this study, the term "prevention" does not necessarily imply that the initiation of breast cancers has been prevented or that the tumors have been permanently eliminated.) The primary aim of the NSABP Breast Cancer Prevention Trial (BCPT; P-1) was to determine whether tamoxifen administered for at least 5 years prevented invasive breast cancer in women at increased risk. Secondary aims were to determine whether tamoxifen administration would lower the incidence of fatal and nonfatal myocardial infarctions and reduce the incidence of bone fractures. Additional objectives were to evaluate breast cancer mortality and tamoxifen's adverse effects in order to assess the benefits and risks from the drug and, in keeping with recent advances, to obtain information with regard to breast cancer genetics.

Tamoxifen was chosen as the agent to be evaluated because of its demonstrated benefit when used alone as well as in combination with chemotherapy to treat advanced breast cancer *(1–5)* and because of its proven efficacy in reducing tumor re-

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See "Notes" following "References."

currence and prolonging survival when administered as postoperative adjuvant therapy in stages I and II disease *(6–10)*. Findings indicating that tamoxifen-treated patients had a statistically significantly lower incidence of contralateral breast cancer *(9–13)* and that most patients used tamoxifen safely with good compliance and minimal side effects also provided justification for its evaluation as a preventive agent *(14)*. Equally compelling was the extensive information related to the drug's pharmacokinetics, metabolism, and antitumor effects that had been observed in experimental animals and humans *(15–18)*. In addition, there was evidence to indicate that tamoxifen interfered with the initiation and promotion of tumors in experimental systems and inhibited the growth of malignant cells by a variety of mechanisms *(19–21)*.

Because tamoxifen had been shown to alter lipid and lipoprotein metabolism *(22–26)*, which could reduce the risk of coronary artery disease, it seemed appropriate that the incidence of and mortality from ischemic heart disease also be assessed. In addition, there was evidence to indicate that, perhaps because of its estrogen agonist activity *(27,28)*, tamoxifen might have a beneficial effect on osteoporosis. Consequently, the decision was made to determine whether tamoxifen reduced the incidence of bone fractures at selected sites.

By September 30, 1997, 13 388 women aged 35 years and older had been randomly assigned in the P-1 trial. Because this number was considered adequate to meet the study objectives as they related to breast cancer, participant entry was terminated. On March 24, 1998, an independent data-monitoring committee, which had provided oversight for the study since its inception, determined that, in accordance with prespecified rules for stopping the study, the findings indicating a reduction in breast cancer risk were sufficiently strong to justify disclosure of the results. This article is the first published report of the findings obtained from the P-1 study.

METHODS

Planning and Initiation of the Trial

In June 1990, the National Cancer Institute (NCI) invited proposals from clinical cooperative groups for a feasibility (pilot) study that, if approved, would permit the design and conduct of a protocol for a breast cancer prevention trial. These proposals were to be reviewed by the Cancer Control Protocol Review Committee in the NCI Division of Cancer Prevention and Control, by the Cancer Therapy Evaluation Program Review Committee, by representatives of the National Heart, Lung, and Blood Institute, and by other NCI/National Institutes of Health staff. In addition, external peer review was to be conducted by an *ad hoc* Special Review Committee convened by the Division of Extramural Activities of the NCI. In February 1991, the NCI and the National Cancer Advisory Board approved the application submitted by the NSABP; on July 3, 1991, the NSABP received approval from the Food and Drug Administration. Investigators from 131 clinical centers throughout the United States and Canada (*see* "Appendix A") were selected by a peer-review process to be contributors to the trial. All investigations conducted were approved by review boards at each institution and were in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services. Each of the 131 clinical centers had on-site auditing to monitor and assess data quality. Screening for breast cancer risk eligibility was initiated on April 22, 1992, and randomization was begun on June 1, 1992.

During the first year of accrual, i.e., from June 1, 1992, through May 31, 1993, nearly half (48%) of the 16 000 women—the number originally projected as being necessary to accomplish the study goal—were accrued to the study. During the last 7 months of 1993 and the first 3 months of 1994, nearly 3300 additional participants were enrolled. Thus, by the end of March 1994, approximately 11 100 women had either been randomly assigned or had agreed to participate in the study. At that time, accrual was interrupted and was not resumed until March 1995. Randomization was completed on September 30, 1997. More detailed information regarding participant accrual has been published *(29)*.

Conditions for Participant Eligibility

Women were deemed acceptable for the P-1 study if they met certain eligibility criteria defined in the protocol and were enrolled at one of the NSABP institutions that had been selected as contributors to the study. To be eligible for the trial, the participants had to have 1) signed a consent document that had been witnessed and dated before randomization; 2) been either 60 years of age or older or between the ages of 35 and 59 years with a 5-year predicted risk for breast cancer of at least 1.66% or had a history of lobular carcinoma *in situ* (LCIS); 3) had a life expectancy of at least 10 years; 4) had a breast examination that demonstrated no clinical evidence of cancer; 5) had a mammogram within 180 days before randomization that showed no evidence of breast cancer; 6) had normal white blood cell and platelet counts and normal hepatic and renal function tests; 7) not been pregnant upon entry into the study or planned not to become pregnant while on protocol therapy; 8) been accessible for follow-up; 9) undergone an endometrial sampling before randomization if they had a uterus and were randomly assigned after July 8, 1994 (Endometrial sampling upon study entry was optional for participants randomly assigned before that date.); 10) taken no estrogen or progesterone replacement therapy, oral contraceptives, or androgens for at least 3 months before randomization; and 11) had no history of deep vein thrombosis or pulmonary embolism.

Breast Cancer Risk Assessment

The algorithm for estimating breast cancer risk was based on the work of Gail et al. *(30)*, who developed a multivariate logistic regression model in which combinations of risk factors were used to estimate the probability of occurrence of breast cancer over time. The variables included in the model were age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. In its original form, the model predicted the combined risk of invasive and noninvasive breast cancers for white women. Making appropriate modifications to account for a different attributable risk, we applied the risk ratio (RR) for each of the parameters used in the Gail model to the expected rates of invasive breast cancer only. Modifications to allow for race-specific determinations of breast cancer risk were also incorporated into the model. The 1984–1988 Surveillance, Epidemiology, and End Results (SEER)[1] rates of invasive breast cancer were used as the expected rates. The total U.S. mortality rates for the year 1988 were used to adjust for the age-specific competing risk of death from causes other than breast cancer.

Risk Benefit

Each woman screened was provided with a risk profile that identified her breast cancer risk and displayed a plot of projected risk over her lifetime (Fig. 1). To enable the women to make a more informed decision about their participation in the trial, each of them received information about the potential number of breast cancer and coronary artery cases that might be prevented from the use of tamoxifen, as well as the number of cases of endometrial cancer and pulmonary embolism that might be caused by the drug.

Statistical Methods

Randomization of participants in a double-blind fashion was performed centrally by the NSABP Biostatistical Center, and participants were stratified by age (35–49 years, 50–59 years, ≥60 years), race (black, white, other), history of LCIS (yes, no), and breast cancer RR (<2.5, 2.5–3.9, ≥4.0). To avoid imbalances in treatment assignment within a clinical center, an adaptive randomization scheme using the biased-coin method of Efron *(31)* was used.

The trial was monitored by an independent data-monitoring committee known as the Endpoint Review, Safety Monitoring and Advisory Committee (ERSMAC), which was composed of representatives with expertise in clinical trial methodology from a variety of disciplines, including oncology, gynecology, cardiology, biostatistics, epidemiology, and research ethics. The design of the study included formal interim monitoring for early stopping based on the primary end point of the trial, i.e., the incidence of invasive breast cancer. The stopping rule of Fleming et al. *(32)* was employed by the use of bounds that used less than 1% of alpha. In addition, as an informal tool to facilitate the monitoring

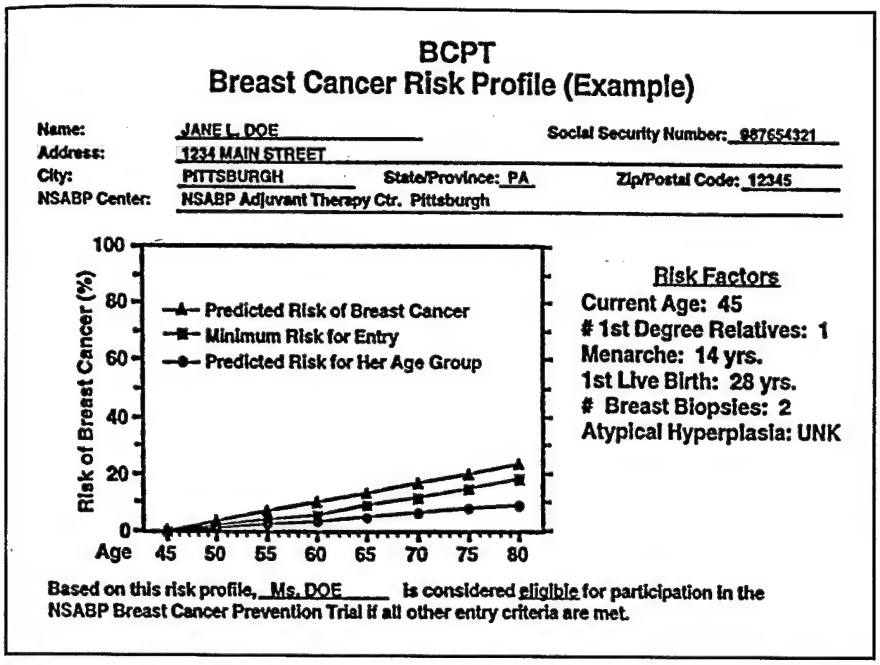

Fig. 1. Example of a breast cancer risk profile. NSABP = National Surgical Adjuvant Breast and Bowel Project; UNK = unknown. (Reproduced from Cancer Control 1997;4:78–86 with permission from the copyright holder.)

of multiple potential beneficial and detrimental outcomes, the ERSMAC adopted a form of global monitoring using a global index modeled after the one proposed by Freedman et al. *(33)* for the Women's Health Initiative trial. The use of this supplemental monitoring tool was not included in the protocol design but was adopted by the ERSMAC before the time of the first formal interim analysis.

All analyses were based on assigned treatment at the time of randomization, regardless of treatment status at the time of analysis. All randomly assigned participants with follow-up were included in the analyses. Average annual event rates for the study end points were calculated for each treatment group by means of a procedure in which the number of observed events was divided by the number of observed event-specific person-years of follow-up. *P* values (two-sided) for tests of differences between the treatment groups for the rates of invasive breast cancer, noninvasive breast cancer, and invasive endometrial cancer were determined by use of the exact method, assuming that the events came from a Poisson distribution and conditioning on the total number of events and the person-years at risk *(34)*. Under these conditions, the expected proportion of events in the tamoxifen group (p) has a binomial distribution and was defined as the number of person-years in the tamoxifen group (PY_{tam}) divided by the total number of person-years in both groups ($PY_{tam} + PY_{plac}$). The observed proportion of events (p_o) was defined as the number of events in the tamoxifen group (n_{tam}) divided by the total number of events in both groups ($n_{tam} + n_{plac}$). The *P* value for testing a difference in the event rates between the groups was then computed as an exact binomial test of the hypothesis that $p = p_o$. Event rates in the two treatment groups were also compared by use of the RR and 95% confidence intervals (CIs), in which the rate in the tamoxifen group was contrasted with that in the placebo group. CIs for RRs were also determined assuming that the events followed a Poisson distribution, conditioning on the total number of events and person-years at risk. Under this circumstance, the CI for an RR was determined by first finding the upper (p_U) and lower (p_L) limits of the CI for p_o, where $p_o = [(\text{RR})\ (PY_{tam})]/[\ (\text{RR})\ (PY_{tam} + PY_{plac})]$ and RR = 1. Then the CI for the RR was determined by solving the equation $\text{RR} = [(p)\ (PY_{plac})]/[(1-p)\ (PY_{tam})]$, where p_U and p_L were substituted as the value of p, respectively. Cumulative incidence rates by follow-up time were determined, accounting for competing risk due to death *(35)*.

Results

Study Screening, Accrual, and Follow-up Information

Breast cancer risk assessments were used to determine the eligibility of women for the study. From April 22, 1992, through May 20, 1997, risk assessments were performed for 98 018 women (Table 1); 57 641 (58.8%) of these women were deemed eligible, on the basis of their risk, for participation in the trial. Of this group, 14 453 women agreed to be medically evaluated for complete eligibility. A total of 13 954 women met all eligibility requirements. Of those, 13 388 (95.9%) were randomly assigned to receive, in a double-blind fashion, 20 mg per day of either tamoxifen or placebo for 5 years; 6707 were to receive placebo, and 6681 were to receive tamoxifen (Table 1). Both tamoxifen and placebo were supplied by Zeneca Pharmaceuticals, Wilmington, DE. After one of the participants had been randomly assigned, it was discovered that she had invasive breast cancer rather than a noninvasive lesion (LCIS), as had originally been reported following mammographic and pathologic examination. Therefore, she was not at risk for development of breast cancer and was not included in the analyses. At the time of analysis, there were 212 participants with no follow-up, 108 in the placebo group and 104 in the tamoxifen group. All of the 13 175 women at risk and with follow-up were included in the analyses. In each study group, 7.2% of the participants withdrew their consent but were followed until consent withdrawal. When the treatment groups were combined, 21.6% of the participants discontinued their assigned therapy for reasons not specified in the protocol. The proportion of women who stopped their therapy was greater in the tamoxifen group, i.e., 19.7% in the placebo group versus 23.7% in the tamoxifen group. Also, 1.6% of the participants in each study group were lost to follow-up. When the consent withdrawals were excluded,

Table 1. Summary of screening, accrual, and follow-up information for the study

Screening, accrual, and follow-up information	Placebo	Tamoxifen	Total
Breast cancer risk assessments	—	—	98 018
Women meeting risk eligibility requirement	—	—	57 641
Medical eligibility assessments	—	—	14 453
Women meeting both risk and medical eligibility requirements	—	—	13 954
Women randomly assigned	6707	6681	13 388
Not at risk for breast cancer*	0	1	1
Without follow-up	108	104	212
Included in analysis	6599	6576	13 175
Average follow-up time, mo	47.7	47.7	47.7
Median follow-up time, mo	54.6	54.5	54.6
% followed for >36 mo	74.0	73.7	73.9
% followed for >48 mo	66.7	67.0	67.0
% followed for >60 mo	37.1	36.4	36.8
Person-years of follow-up†	26 247	26 154	52 401

**See* text for details.
†Based on time at risk for death.

the percent of participants with complete follow-up was 92.4% in the placebo group and 92.3% in the tamoxifen group. The study was designed to maintain statistical power even if the rate of noncompliance, defined as permanently discontinuing tamoxifen therapy, was as high as 10% per year of follow-up. While the cumulative rate of noncompliance was below the planned level, the interruption of accrual in 1994 resulted in a substantial increase in the rates of noncompliance and of consent withdrawal. In the 6-month interval following the interruption, the proportion of women who became noncompliant or who withdrew their consent was two to three times higher than before or after that interval.

The mean time on the study for the 13 175 participants who were included in the analysis was 47.7 months; 73.9% had a follow-up exceeding 36 months, 67.0% were followed for more than 48 months, and 36.8% had follow-up exceeding 60 months. The median follow-up time was 54.6 months. All data included in this article are based on information received as of July 31, 1998, concerning follow-up through March 31, 1998. This was the cutoff point selected because it was the day before the trial was unblinded. On April 1, 1998, investigators were provided with lists identifying the treatment assignment for each participant.

Participant Characteristics

Of the 13 175 participants included in the analysis, 39.3% were 35–49 years old at randomization, 30.7% were 50–59 years old, and 30.0% were 60 years of age or older (Table 2). Only 2.6% of the participants were 35–39 years of age, and 6.0% were 70 years of age or older. Almost all participants were white (96.4%), more than one-third (37.1%) had had a hysterectomy, 6.3% had a history of LCIS, and 9.1% had a history of atypical hyperplasia. The distribution of participants among the placebo and tamoxifen groups relative to these characteristics was similar.

Almost one fourth (23.8%) of the participants had no first-degree relatives with breast cancer. More than one half (56.8%) had one first-degree relative with breast cancer, 16.4% had two, and 3.0% had three or more. About one quarter of the women had a 5-year predicted breast cancer risk that was 2.00% or less. Almost three fifths (57.6%) had a 5-year risk between 2.01% and 5.00%, and 17.4% had a risk of more than 5.00%.

Breast Cancer Events

A total of 368 invasive and noninvasive breast cancers occurred among the 13 175 participants; 244 of these occurred in the placebo group and 124 in the tamoxifen group (Fig. 2). There was a highly significant reduction in the incidence of breast cancer as a result of tamoxifen administration; that decrease was observed for both invasive and noninvasive disease. For invasive breast cancer, there was a 49% reduction in the overall risk. There were 175 cases of invasive breast cancer in the placebo group, as compared with 89 in the tamoxifen group ($P<.00001$). The cumulative incidence through 69 months was 43.4 per 1000 women and 22.0 per 1000 women in the two groups, respectively. For noninvasive breast cancer, the reduction in risk was 50%; there were 69 cases in women receiving placebo and 35 in those receiving tamoxifen ($P<.002$). Through 69 months, the cumulative incidence of noninvasive breast cancer among the placebo group was 15.9 per 1000 women versus 7.7 per 1000 women in the tamoxifen group. The average annual rate of noninvasive breast cancer per 1000 women was 2.68 in the placebo group compared with 1.35 in the tamoxifen group, yielding an RR of 0.50 (95% CI = 0.33–0.77). The reduction in noninvasive cancers related to a decrease in the incidence of both ductal carcinoma *in situ* (DCIS) and LCIS. No survival differences were observed. Nine deaths were attributed to breast cancer, i.e., six in the group that received placebo and three in the tamoxifen group.

To assess the consistency of the effect of tamoxifen across the population, rates of invasive breast cancer were calculated for several subgroups of women. When age, history of LCIS, history of atypical hyperplasia, and levels of predicted risk of breast cancer were taken into consideration, tamoxifen was found to be effective in preventing breast cancer in all subgroups (Table 3). The reduction in the incidence of invasive breast cancer associated with tamoxifen ranged from 44% among women who were 49 years of age or younger at the time of randomization to 55% among those who were 60 years of age or older at randomization. Among women with a history of LCIS, the reduction in risk was 56%. The reduction was particularly noteworthy among those with a history of atypical hyperplasia—there were 23 cases

Table 2. Participant characteristics at time of randomization for women included in the analyses

	Placebo		Tamoxifen	
Characteristic	No.	%	No.	%
Age, y				
35–39	185	2.8	159	2.4
40–49	2411	36.5	2422	36.8
50–59	2017	30.6	2031	30.9
60–69	1590	24.1	1571	23.9
≥70	396	6.0	393	6.0
Race				
White	6359	96.4	6347	96.5
Black	111	1.7	109	1.7
Other	129	2.0	120	1.8
No. of first-degree relatives with breast cancer				
0	1595	24.2	1540	23.4
1	3731	56.5	3754	57.1
2	1092	16.5	1069	16.3
≥3	181	2.7	213	3.2
Prior hysterectomy				
No	4194	63.6	4097	62.3
Yes	2405	36.4	2479	37.7
History of lobular carcinoma *in situ*				
No	6188	93.8	6161	93.7
Yes	411	6.2	415	6.3
History of atypical hyperplasia in the breast				
No	5985	90.7	5997	91.2
Yes	614	9.3	579	8.8
5-y predicted breast cancer risk, %				
≤2.00	1660	25.2	1636	24.9
2.01–3.00	2031	30.8	2057	31.3
3.01–5.00	1791	27.1	1714	26.1
≥5.01	1117	16.9	1169	17.8
Total	6599	100.0	6576	100.0

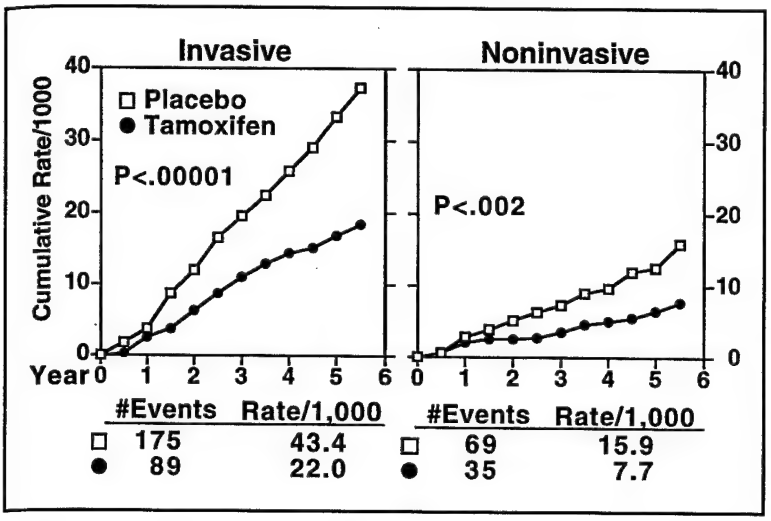

Fig. 2. Cumulative rates of invasive and noninvasive breast cancers occurring in participants receiving placebo or tamoxifen. The *P* values are two-sided.

of invasive breast cancer in the placebo group and three in the tamoxifen group. When related to the level of predicted risk among participants, the reduction of cancer risk ranged from 32% to 66%. Because the proportion of nonwhite women randomly assigned in the trial was small (3.6%), only nine invasive breast cancer events were observed in this population. Seven events occurred in black women and two in women of other races. Of the seven tumors that occurred among blacks, two were in the placebo group and five were in the tamoxifen group.

The effectiveness of tamoxifen in preventing invasive breast cancer was assessed by means of a comparison of the rates of the occurrence of that disease during each of the first 6 yearly intervals of follow-up (Fig. 3). When the average annual rate per 1000 women in the placebo group was compared with that in the tamoxifen group, there was a substantial reduction in risk for each year of follow-up in the latter group. The observed rates of reduction by year were 33%, 55%, 39%, 49%, 69%, and 55%.

Tumor Characteristics

Rates of invasive breast cancer by selected tumor characteristics are compared in Fig. 4. The annual rate of estrogen receptor (ER)-positive breast cancers was 69% less in women in the tamoxifen group. The rates were 5.02 per 1000 women in the placebo group compared with 1.58 per 1000 women in the tamoxifen group (RR = 0.31; 95% CI = 0.22–0.45). There was no evidence of a significant difference in the rates of tumors presenting as ER-negative (1.20 per 1000 women in the placebo group and 1.46 per 1000 women in the tamoxifen group; RR = 1.22; 95% CI = 0.74–2.03). Of the seven invasive breast cancers that occurred among black women, four were ER negative and three were ER positive. Of those that were ER positive, two were in the placebo group and one was in the tamoxifen group.

The rate of invasive breast cancer among women in the tamoxifen group was less than that among women in the placebo group in all tumor-size categories. The greatest difference between treatment groups was evident in the occurrence of tumors that were 2.0 cm or less in size at the time of diagnosis. The observed rates of occurrence of tumors of 1.0 cm or smaller were 2.43 per 1000 women in the placebo group and 1.43 per 1000 women in the tamoxifen group. The rates of occurrence of tumors 1.1–2.0 cm were 2.63 and 1.04 per 1000 women, respectively. The rates of occurrence of tumors of 2.1–3.0 cm were 0.85 per 1000 women in the placebo group and 0.54 per 1000 women in the tamoxifen group; for tumors 3.1 cm or larger, the rates were 0.73 and 0.42 per 1000 women, respectively.

Table 3. Average annual rates for invasive breast cancer by age, history of lobular carcinoma *in situ* (LCIS), history of atypical hyperplasia, 5-year predicted breast cancer risk, and number of first-degree relatives with breast cancer

Patient characteristic	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
All women	175	89	6.76	3.43	0.51	0.39–0.66
Age, y						
≤49	68	38	6.70	3.77	0.56	0.37–0.85
50–59	50	25	6.28	3.10	0.49	0.29–0.81
≥60	57	26	7.33	3.33	0.45	0.27–0.74
History of LCIS						
No	157	81	6.41	3.30	0.51	0.39–0.68
Yes	18	8	12.99	5.69	0.44	0.16–1.06
History of atypical hyperplasia						
No	152	86	6.44	3.61	0.56	0.42–0.73
Yes	23	3	10.11	1.43	0.14	0.03–0.47
5-y predicted breast cancer risk, %						
≤2.00	35	13	5.54	2.06	0.37	0.18–0.72
2.01–3.00	42	29	5.18	3.51	0.68	0.41–1.11
3.01–5.00	43	27	5.88	3.88	0.66	0.39–1.09
≥5.01	55	20	13.28	4.52	0.34	0.19–0.58
No. of first-degree relatives with breast cancer						
0	38	17	6.45	2.97	0.46	0.24–0.84
1	90	46	6.00	3.03	0.51	0.35–0.73
2	37	20	8.68	4.75	0.55	0.30–0.97
≥3	10	6	13.72	7.02	0.51	0.15–1.55

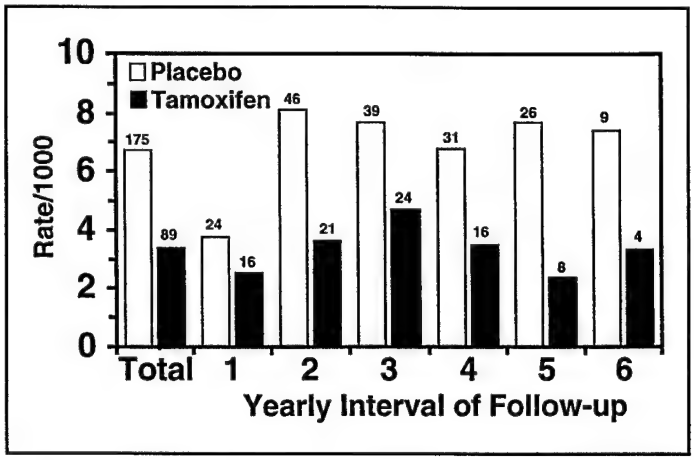

Fig. 3. Rates of invasive breast cancer occurring in participants receiving placebo or tamoxifen, by yearly interval of follow-up. Numbers above the bars indicate numbers of events.

The rate of invasive breast cancer by nodal status at the time of diagnosis differed in the two treatment groups. Because axillary dissection was not performed for all cases of invasive breast cancer, pathologic nodal status was not available for 12 women in the placebo group and for three women in the tamoxifen group. The rates of breast cancers presenting without nodal involvement were 4.48 and 2.31 per 1000 women in the placebo and tamoxifen groups, respectively. The rates of occurrence of tumors presenting with one to three involved nodes were 1.39 and 0.54 per 1000 women, respectively. The rates for cancers presenting with four or more positive axillary nodes were the same in both study groups.

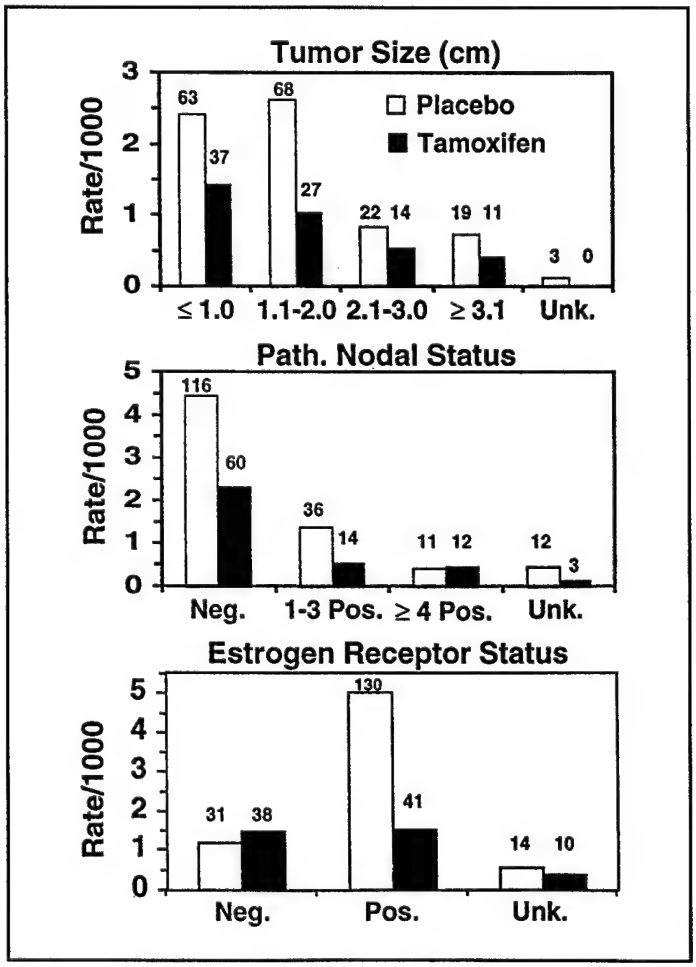

Fig. 4. Rates of invasive breast cancer occurring in participants receiving placebo or tamoxifen, by tumor size, lymph node status, and estrogen receptor status. Numbers above the bars indicate numbers of events. UNK. = unknown; Path. = pathologic; Neg. = negative; Pos. = positive.

Endometrial Cancer

Participants who received tamoxifen had a 2.53 times greater risk of developing an invasive endometrial cancer (95% CI = 1.35–4.97) than did women who received placebo, an average annual rate per 1000 participants of 2.30 in the former group and 0.91 in the latter group (Table 4). The increased risk was predominantly in women 50 years of age or older. The RR of women aged 49 years or younger was 1.21 (95% CI = 0.41–3.60), whereas it was 4.01 (95% CI = 1.70–10.90) in women aged 50 years or older. The increase in incidence after tamoxifen administration was observed early in the follow-up period (Fig. 5). Through 66 months of follow-up, the cumulative incidence was 5.4 per 1000 women and 13.0 per 1000 women in the placebo and tamoxifen groups, respectively. Fourteen (93%) of the 15 invasive endometrial cancers that occurred in the placebo group were International Federation of Gynecology and Obstetrics (FIGO) stage I, and one (7%) was FIGO stage IV. All 36 invasive endometrial cancers that occurred in the group receiving tamoxifen were FIGO stage I. Four *in situ* endometrial cancers were reported; three of these occurred in the placebo group and one in the tamoxifen group.

Invasive Cancers Other Than Cancer of the Breast and Uterus (Endometrium)

Invasive cancers at sites other than the breast and endometrium were equally distributed, with 97 cases in each group (RR = 1.00; 95% CI = 0.75–1.35) (Table 5). At no site was there evidence of a disproportionate number of events. Of particular importance were the observations that no liver cancers occurred in either group and that there was no increase in the incidence of colon, rectal, ovarian, or other genitourinary tumors. The greatest incidence of tumors occurred in the lung, trachea, and bronchus (17 in the placebo group and 20 in the tamoxifen group).

Ischemic Heart Disease

Women who experienced more than one ischemic heart disease event were categorized according to the most severe event in decreasing order from fatal myocardial infarction to acute ischemic syndrome. The number of participants who had a myocardial infarction in the placebo and tamoxifen groups was 28 and 31, respectively. Eight (29%) of the 28 events that occurred in the placebo group were fatal, as compared with seven (23%) of the 31 events in the group that received tamoxifen (Table 6). Likewise, the number of participants who had angina requiring a coronary artery bypass graft or angioplasty was 14 in the placebo group and 13 in the tamoxifen group. The number of women reported as having acute ischemic syndrome was 20 in the placebo group and 27 in the tamoxifen group (RR = 1.36; 95% CI = 0.73–2.55). Of the total number of events related to ischemic heart disease, 62 occurred in the placebo group (five in women aged ≤49 years and 57 in women aged ≥50 years); 71 events occurred in the tamoxifen group (10 and 61 in the two age

Table 4. Average annual rates of invasive and *in situ* endometrial cancer

Type of event	No. of events		Rate per 1000 women*		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Invasive cancer	15	36	0.91	2.30	2.53	1.35–4.97
Age, y						
≤49	8	9	1.09	1.32	1.21	0.41–3.60
≥50	7	27	0.76	3.05	4.01	1.70–10.90
In situ cancer	3	1	0.18	0.06	0.35	0.01–4.38

*Women at risk; nonhysterectomized.

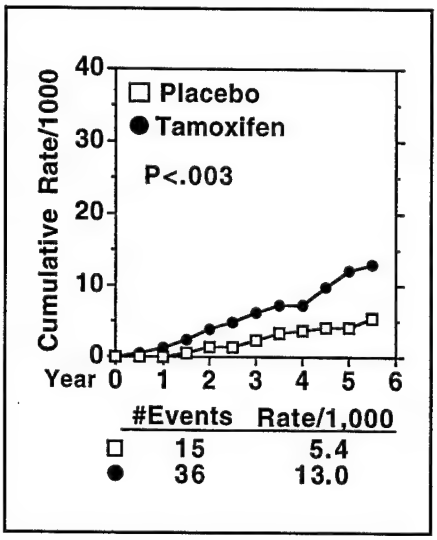

Fig. 5. Cumulative rates of invasive endometrial cancer occurring in participants receiving placebo or tamoxifen. The *P* value is two-sided.

Table 5. Distribution of invasive cancers other than breast and uterine (endometrial) cancer

Primary cancer site*	No. of cancers	
	Placebo	Tamoxifen
Mouth, pharynx, larynx	2	3
Stomach	2	1
Gallbladder	1	0
Pancreas	7	4
Retroperitoneum	1	0
Colon	9	11
Rectum	3	4
Liver	0	0
Lung, trachea, bronchus	17	20
Lymphatic, hematopoietic systems	11	14
Ovary/fallopian tube	11	10
Other genital	4	4
Urinary bladder	1	3
Kidney	3	2
Connective tissue	2	1
Skin	9	11
Nervous system	3	1
Thyroid gland	5	4
Unknown	6	4
Total	97	97
Average annual rate per 1000 women	3.72	3.73
Risk ratio (95% confidence interval)	1.00 (0.75–1.35)	

*International Classification of Diseases code 9 *(68)*.

groups, respectively). Overall, the average annual rate of ischemic heart disease was 2.37 per 1000 women in the placebo group and 2.73 per 1000 women in the tamoxifen group.

Fractures

Fractures of the hip and radius (Colles') were defined in the protocol as the primary fracture events to be evaluated in the trial. Soon after initiation of the study, fractures of the spine were also included. These three fracture sites were selected *a priori* as those that would most likely be associated with osteoporosis. Also, when the radiology reports were reviewed to identify fractures of the radius that were Colles' fractures, it became evident that, without the actual x-ray films, it was difficult to determine whether some of the lower radial fractures were Colles' or not. Thus, to ensure that reporting was complete, a fourth category of fractures, i.e., fractures of the lower radius other than Colles', was included. A total of 955 women experienced bone fractures, 483 and 472 in the placebo and tamoxifen groups, respectively. Fewer osteoporotic fracture events (combined hip, spine, and lower radius) occurred in women who received tamoxifen than in those who received placebo. Overall, 111 women in the tamoxifen group experienced fractures at one or more of these sites, as compared with 137 women in the placebo group; this represents a 19% reduction in the incidence of fractures, a reduction that almost reached statistical significance (RR = 0.81; 95% CI = 0.63–1.05) (Table 7). There was a 45% reduction in fractures of the hip (RR = 0.55; 95% CI = 0.25–1.15), a 39% reduction in Colles' fractures (RR = 0.61; 95% CI = 0.29–1.23), no reduction in other lower radial fractures (RR = 1.05; 95% CI = 0.73–1.51), and a 26% reduction in fractures of the spine (RR = 0.74; 95% CI = 0.41–1.32). The overall reduction was greater in the older age group (≥50 years at entry) (RR = 0.79; 95% CI = 0.60–1.05).

Vascular Events

Women who experienced both a stroke and a transient ischemic attack or both a pulmonary embolism and a deep vein thrombosis were categorized according to the most severe event, i.e., stroke or pulmonary embolism, respectively. While not statistically significant at the traditional level (95% CI), the incidence of stroke increased from 24 events in the placebo group to 38 events in the tamoxifen group, i.e., from 0.92 per 1000 participants per year in the former group to 1.45 per 1000 participants per year in the latter group (Table 8). The RR was 1.59, and the 95% CI was 0.93–2.77. Fourteen of the 24 strokes that occurred in the placebo group were reported as being the result of vascular occlusion, and six were considered to be hemor-

Table 6. Average annual rates of ischemic heart disease

Type of event	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Myocardial infarction*	28	31	1.07	1.19	1.11	0.65–1.92
Fatal	8	7	0.30	0.27	0.88	0.27–2.77
Nonfatal	20	24	0.76	0.92	1.20	0.64–2.30
Severe angina†	14	13	0.53	0.50	0.93	0.40–2.14
Acute ischemic syndrome‡	20	27	0.77	1.03	1.36	0.73–2.55
Total	62	71	2.37	2.73	1.15	0.81–1.64

*International Classification of Diseases codes 410–414 *(68)*.

†Requiring angioplasty or coronary artery bypass graft.

‡New Q-wave on electrocardiogram without angina or elevation of serum enzymes or angina requiring hospitalization without surgery.

Table 7. Annual rates for fracture events among participants

Site of fracture	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Hip	22	12	0.84	0.46	0.55	0.25–1.15
Spine	31	23	1.18	0.88	0.74	0.41–1.32
Radius, Colles'	23	14	0.88	0.54	0.61	0.29–1.23
Other lower radius*	63	66	2.41	2.54	1.05	0.73–1.51
Total	137†	111‡	5.28	4.29	0.81	0.63–1.05
≤49 y of age at entry	23	20	2.24	1.98	0.88	0.46–1.68
≥50 y of age at entry	114	91	7.27	5.76	0.79	0.60–1.05

*Excludes women who had a Colles' fracture.

†One woman had a hip fracture and a Colles' fracture, and one woman had a hip fracture and another lower radial fracture.

‡One woman had a hip fracture and a Colles' fracture, one woman had a hip fracture and a spine fracture, and two women had hip fractures and other lower radial fractures.

Table 8. Average annual rates of vascular-related events by age at study entry

Type of event by age at entry	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Stroke*	24	38	0.92	1.45	1.59	0.93–2.77
≤49 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	20	35	1.26	2.20	1.75	0.98–3.20
Transient ischemic attack	25	19	0.96	0.73	0.76	0.40–1.44
≤49 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	21	16	1.32	1.01	0.76	0.37–1.53
Pulmonary embolism†	6	18	0.23	0.69	3.01	1.15–9.27
≤49 y old	1	2	0.10	0.20	2.03	0.11–119.62
≥50 y old	5	16	0.31	1.00	3.19	1.12–11.15
Deep vein thrombosis‡	22	35	0.84	1.34	1.60	0.91–2.86
≤49 y old	8	11	0.78	1.08	1.39	0.51–3.99
≥50 y old	14	24	0.88	1.51	1.71	0.85–3.58

*Seven cases were fatal (three in the placebo group and four in the tamoxifen group).

†Three cases in the tamoxifen group were fatal.

‡All but three cases in each group required hospitalization.

rhagic in origin. The etiology of four was unknown. Two deaths occurred in women who had the occlusive type, and one death occurred in a woman who had a stroke that was hemorrhagic in origin. Of the 38 strokes that occurred in the group receiving tamoxifen, 21 were occlusive, 10 were hemorrhagic in origin, and seven were of unknown etiology. Three of the hemorrhagic strokes were fatal. One death occurred among the seven women who experienced stroke of unknown etiology. Thus, three of the deaths that occurred in the placebo group and four that occurred in the tamoxifen group were related to stroke. When the distribution of strokes was examined according to age, the number of events in women aged 49 years or younger was similar, i.e., four in the placebo group and three in the tamoxifen group. Among women aged 50 years or older, 20 strokes occurred in those who received placebo and 35 in those who received tamoxifen. In that age group, the RR was 1.75, and the 95% CI was 0.98–3.20.

Twenty-five transient ischemic attacks occurred in the placebo group and 19 in the tamoxifen group (Table 8).

Pulmonary emboli were observed in almost three times as many women in the tamoxifen group as in the placebo group (18 versus six; RR = 3.01; 95% CI = 1.15–9.27) (Table 8). When the incidence of pulmonary embolism was related to the age of participants, there was an increase in those events in postmenopausal women who received tamoxifen. In women aged 49 years or younger, one event occurred in the placebo group and two events occurred in the tamoxifen group (RR = 2.03; 95% CI = 0.11–119.62); in contrast, in those aged 50 years or older, five events occurred in the former group and 16 in the latter group (RR = 3.19; 95% CI = 1.12–11.15).

More women who received tamoxifen developed deep vein thrombosis than did women who received placebo (35 versus 22 cases, respectively) (Table 8). The average annual rates per 1000 women were 1.34 versus 0.84 (RR = 1.60; 95% CI = 0.91–2.86). The excess risk appeared to be greater among women aged 50 years or older. For women aged 49 years or younger, the number of cases was eight in the placebo group versus 11 in the tamoxifen group (RR = 1.39; 95% CI = 0.51–3.99). In women 50 years of age or older, the number of cases was 14 versus 24, with an RR of 1.71 (95% CI = 0.85–3.58).

Cataracts

More than 1.5 years before the trial was stopped and the treatment assignments were unblinded (October 1996), the ERSMAC released information to the NSABP leadership with regard to an excess risk of cataracts and cataract surgery observed among women in the tamoxifen group. The NSABP leadership then informed officials of the NCI, the Office for Protection From Research Risks, and the principal investigators and participants in the trial. It was also provided (by the NCI) to chairpersons of the local Institutional Review Boards responsible for oversight of all breast cancer treatment trials in which tamoxifen was administered. The status regarding these outcomes at the time of this analysis is summarized in Table 9. Information on the development of cataracts was based on unconfirmed self-reporting. However, information regarding cataract surgery was verified and documented by examination of medical records. The rate of cataract development among women who were cataract-free at the time of randomization was 21.72 per 1000 women in the placebo group and 24.82 per 1000 women in the tamoxifen group. This represents an RR of 1.14, with CIs that indicate marginal statistical significance (95% CI = 1.01–1.29). There was also a difference by treatment group with respect to cataract surgery. In the placebo and tamoxifen groups, the rates of developing cataracts and undergoing cataract surgery were 3.00 and 4.72 per 1000 women, respectively (RR = 1.57; 95% CI = 1.16–2.14). A total of 943 women reported having cataracts at entry into the study. The RR of cataract surgery in these women was similar to that experienced by women who developed cataracts after randomization. This excess risk was observed primarily among women in the older age group.

Quality of Life

At each follow-up visit, participants were evaluated relative to tamoxifen-related, non-life-threatening side effects that could affect their quality of life. Information was collected with regard to the occurrence of hot flashes, vaginal discharge, irregular menses, fluid retention, nausea, skin changes, diarrhea, and weight gain or loss. A self-administered depression scale developed by the Center for Epidemiological Studies (CES-D) *(36)* was used to estimate the relation of tamoxifen to the occurrence of mental depression. Also self-reported at each visit were data from the Medical Outcomes Study Short Form 36 (MOSSF-36) and the Medical Outcomes Study (MOS) Sexual Functioning Scale *(37)*.

The only symptomatic differences noted between the placebo and tamoxifen groups were related to hot flashes and vaginal discharge, both of which occurred more often in the latter group (Table 10). The proportion of women who reported hot flashes as being quite a bit or extremely bothersome was 45.7% in the tamoxifen group, as compared with 28.7% in the placebo group. The proportion reporting vaginal discharge that was moderately bothersome or worse was 29.0% in the tamoxifen group, as compared with 13.0% in the placebo group. There were no notable differences between the two groups relative to any of the findings obtained from the various self-reporting instruments. Of particular note are the findings for depression scores determined from the CES-D scale. The distribution of participants in the two groups according to the various levels of clinical depression was almost identical. The highest depression score observed was less than or equal to 15 for 65.4% of the women in each group, and the proportion of women with a score that was greater than or equal to 30 was 9.0% in the placebo group and 8.8% in the tamoxifen group. The findings regarding quality of life will be presented in a subsequent publication.

Causes and Demographics of Deaths

Seventy-one deaths occurred among participants in the placebo group and 57 occurred among women in the tamoxifen group (RR = 0.81; 95% CI = 0.56–1.16) (Table 11). Forty-two deaths in the placebo group and 23 deaths in the tamoxifen group were due to cancer. Aside from the breast, uterus, ovary, and lung, a small number of deaths were related to cancer occurring at a variety of other sites, such as the brain, colon, pancreas,

Table 9. Average annual rates of cataracts and cataract surgery among participants

Status of participants	No. of women		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Without cataracts at randomization	6131	6101	—	—		
Developed cataracts	507	574	21.72	24.82	1.14	1.01–1.29
Developed cataracts and underwent cataract surgery	73	114	3.00	4.72	1.57	1.16–2.14

Table 10. Distribution of participants in the placebo and tamoxifen groups by highest level of hot flashes, vaginal discharge, and depression reported*

Symptom	% of participants	
	Placebo (n = 6498)	Tamoxifen (n = 6466)
Hot flashes, bothersome		
No	31.4	19.4
Slightly	18.2	14.1
Moderately	21.7	21.8
Quite a bit	18.6	28.1
Extremely	10.1	17.6
Vaginal discharge, bothersome		
No	65.2	44.8
Slightly	21.8	26.2
Moderately	8.5	16.6
Quite a bit	3.3	9.3
Extremely	1.2	3.1
Depression (CES-D)†		
0–15	65.4	65.4
16–22	16.1	15.6
23–29	9.5	10.1
30–36	5.4	5.1
≥37	3.6	3.7

*The quality-of-life questionnaire that was used was a self-reporting instrument. Some participants opted not to complete the questionnaires. Thus, information is not available for 101 women in the placebo group and 110 in the tamoxifen group.

†CES-D refers to a self-administered depression scale developed by the Center for Epidemiological Studies *(36)*.

Table 11. Distribution of causes of death

Cause	No. of deaths	
	Placebo	Tamoxifen
Cancer	42	23
Brain	3	1
Breast	6	3
Colon	1	1
Uterus (endometrium)	1	0
Lung	11	8
Ovary	1	2
Lymphatic system	4	2
Pancreas	6	2
Extrahepatic bile duct	1	0
Kidney	2	0
Melanoma	0	1
Thyroid gland	1	0
Primary site unknown	5	3
Cardiac and vascular disease	15	22
Heart disease (ischemic and other)	12	13
Stroke	3	4
Pulmonary embolus	0	3
Arterial disease	0	2
Other	14	12
Amyotrophic lateral sclerosis	2	0
Automobile accident	2	1
Miscellaneous (11 different causes)	6	7
Unknown	4	4
Total deaths	71	57
Average annual rate per 1000 women	2.71	2.17
Risk ratio (95% confidence interval)	0.81 (0.56–1.16)	

thyroid gland, and kidney. Fifteen deaths in the placebo group and 22 deaths in the tamoxifen group were from causes related to the vascular system. Four women died of stroke in the tamoxifen group, whereas three women died of stroke in the placebo group. Two women in the tamoxifen group and none in the placebo group died of arterial disease other than stroke. Three women in the tamoxifen group and none in the placebo group died as a result of pulmonary embolism.

Discussion

Although, in the past, consideration had been given to primary prevention, the aim of which was to prevent cancer by identifying and eliminating cancer-causing agents, and to secondary prevention, which involved screening individuals at increased risk for cancer in the hope that early detection and treatment would affect survival, it was not until the mid-1980s that serious attention was given to chemoprevention, an approach aimed at reducing cancer risk by the administration of natural or synthetic clinical compounds that prevent, reverse, or suppress carcinogenesis in individuals at increased risk for the disease *(38)*. Although biologic and clinical considerations related to chemoprevention have received much attention *(39–41)*, almost no studies have been directed toward evaluating the concept as it relates to breast cancer. Although information obtained in the 1980s provided support for the theory that dietary fat might be associated with the occurrence of breast cancer and that restricting fat intake could perhaps reduce the incidence of the disease *(42)*, a trial to test that hypothesis has only recently been implemented. The use of retinoids for the prevention of breast cancer began to receive attention in 1987, when a study was initiated to evaluate the effectiveness of fenretinide (4-HPR) *(43)*. To date, as far as we are aware, no information with regard to breast cancer end points has been reported from that trial.

The findings in this article provide the first information from a randomized clinical trial to support the hypothesis that breast cancer can be prevented in a population of women at increased risk for the disease. They show that tamoxifen administration reduced the risk of invasive and noninvasive breast cancers by almost 50% in all age groups. Of particular importance is the finding that a benefit from tamoxifen was identified among women at various levels of risk within the spectrum of risks associated with participants in the P-1 study.

Because of the importance of knowing whether or not the finding that tamoxifen reduces the incidence of tumors can be generalized to all women, extensive effort was directed toward recruiting nonwhite participants. Despite great effort, the number of nonwhite participants was small, and there were few events among those women. For these reasons, the size of the treatment effect estimated from the total population (49% reduction of breast cancer risk) may not be a reliable estimate for nonwhite women.

Also of importance are the findings obtained in women who had a history of LCIS or atypical hyperplasia, pathologic entities thought to increase the risk of invasive breast cancer. Although the present study was not designed to address these issues, it provides the only quantitative information available from a clinical trial about the magnitude of the risk of invasive cancer in women with a reported history of LCIS or atypical hyperplasia

and presents the only information to demonstrate that tamoxifen can reduce the magnitude of that risk. When compared with women who had no history of LCIS or atypical hyperplasia, the finding of a 100% increase in the average annual rate of invasive cancer among women in the placebo group who had a history of LCIS and of a nearly 57% increase in this rate among women with a history of atypical hyperplasia clearly indicates that these pathologic entities are associated with a substantial increase in a woman's risk for invasive breast cancer. Even more important is the finding that tamoxifen administration dramatically reduced the risk of invasive cancer in women with a history of LCIS or atypical hyperplasia.

Although the findings indicating the extent to which the invasive cancer risk was reduced are compelling, the occurrence of a 50% reduction in the risk of noninvasive breast cancer is equally important for the following reasons. The expanded use of mammography has resulted in the more frequent detection of DCIS. In view of the cost involved and the effort required to diagnose these tumors and in light of the debate about both the initial and subsequent treatment of patients with DCIS and the putative relationship between DCIS and the subsequent occurrence of invasive breast cancer, a reduction in the risk of DCIS must be viewed as an important finding, since prevention of that disease would obviate the above considerations. Moreover, the reduction in the incidence of DCIS provokes consideration of the biologic significance of that finding. Cells comprising most DCIS lesions have been demonstrated to be ER positive *(44,45)*. Consequently, if DCIS is, indeed, a precursor of invasive cancer, at least some of the invasive tumors that were prevented by tamoxifen in the P-1 study could be the result of the elimination of occult DCIS by the drug. In that regard, the findings regarding the characteristics of the invasive breast cancers that occurred among the participants in the P-1 study are of importance. When the findings from tumors that occurred in the two groups were compared, it was observed that, in the tamoxifen group, there was a decreased rate of invasive cancers that were ER positive, that were 2.0 cm or less in size, or that were associated with negative lymph nodes. These observations provide insight relative to the biologic nature of the tumors that were prevented. These findings are consistent with the thesis that the benefit from tamoxifen results from its inhibition of the growth and progression of tumors that are ER positive, i.e., those that are more likely to exhibit slower growth and less likely to be associated with axillary nodal involvement. It is also of interest that LCIS and atypical hyperplasia are, most often, ER positive *(46,47)* and that there was a marked reduction in tumors that occurred in women with a history of those lesions. In view of these findings, a question to be answered relates to when cells in the biologic cascade of events leading from tumor initiation to the phenotypic expression of invasive tumors express their ER status and, thus, may be affected by tamoxifen.

Although the P-1 study was not designed to have the power to evaluate specifically the hypothesis that tamoxifen reduced the rate of heart disease, a secondary goal was to obtain information regarding the incidence of fatal and nonfatal myocardial infarctions. When the study was being designed, there was evidence that tamoxifen altered lipid and lipoprotein metabolism *(22–26)*. However, information about tamoxifen's effect on the cardiovascular system that had been obtained from clinical trials employing the drug for the treatment of breast cancer was inconclusive. The P-1 study findings that failed to demonstrate that tamoxifen reduced the risk of and mortality from ischemic heart disease differ from those obtained in the Stockholm *(48)* and the Scottish *(49)* studies, in which it was reported that tamoxifen reduced cardiac morbidity in breast cancer patients. These findings are similar, however, to those observed in the NSABP B-14 trial. In that study *(50)*, although there was a trend that suggested the possibility of such an effect, statistically significant differences in cardiovascular mortality were not observed in tamoxifen-treated patients. Thus, although tamoxifen can improve lipid profiles, its effect on the reduction of cardiovascular disease in women taking the drug remains uncertain. While the current findings suggest that tamoxifen does not play a role in preventing ischemic heart disease, they do show that, at least during the duration of the P-1 study, the drug did not have a detrimental effect on the heart.

One of the original aims of the P-1 study was to determine whether tamoxifen reduced the risk of fractures of the hip, radius (Colles'), and spine. The current findings indicating a 45%, 39%, and 26% reduction in fractures at those sites cannot be viewed as inconsequential. When considered in light of the estimate made in 1990 that 24 million American women suffer from osteoporosis, that 1.3 million fractures per year occur secondary to that disease, and that the estimate of the cost of treating such patients is $6.1 billion per year, the prevention of fractures is important for women at increased risk for breast cancer who are also at risk for osteoporosis as they age *(51)*. Because the findings with regard to fractures are based on a relatively small number of events, definitive conclusions relative to the effect of tamoxifen on the rate of fractures must await additional information.

Whether the benefit achieved from tamoxifen in the P-1 study was due to the drug's interference with the initiation and promotion of tumors or to hindrance of the growth of occult tumors is unknown. Because it is likely that a broad spectrum of molecular–biologic and pathologic changes in breast tissue existed among participants at the time of their entry into the trial, it might be assumed that both mechanisms were responsible for the finding. Nonetheless, the absence of specific information to resolve the issue does not detract from the evidence indicating that tamoxifen did, in fact, prevent the clinical expression of tumors, i.e., the goal of primary disease prevention.

The length of tamoxifen administration is another concern. It has been speculated that tamoxifen administration for only 5 years may merely delay tumor growth for a short time and that, if the drug fails to affect the process of tumor initiation and promotion, tumors will subsequently appear. In view of the time required for a tumor to become clinically evident, another concern that has been raised is that the administration of tamoxifen for only 5 years may be inadequate. Information from NSABP B-14, which indicated that the benefit from 5 years of tamoxifen administered to women with stage I ER-positive tumors remained through 10 years of follow-up, fails to support that concern *(52)*. Since the findings in that study also demonstrated that more than 5 years of tamoxifen did not enhance the drug's effect, in the P-1 study the drug was administered for only 5 years. However, additional studies with more prolonged tamoxifen administration and follow-up time are necessary before a hypothetical issue such as this one can be resolved.

Another question that has been raised by the study results relates to the timing of tamoxifen administration. In women at sufficient risk for receiving the drug, the issue of timing should not be considered critical. On the other hand, it is likely that the biologic changes that occurred in breast cells were present when participants who subsequently developed tumors were enrolled in the trial. Consequently, it is not unexpected that such tumors began to be diagnosed early in the follow-up period. Thus, it does not seem justified to delay administration of the drug to women such as those in the P-1 study who were at increased risk for breast cancer.

It is appropriate to consider whether the benefit from tamoxifen in reducing the incidence of breast cancer is sufficiently great to justify its use as a chemopreventive agent despite the risk of undesirable side effects. From the onset of the P-1 study, there has been considerable emphasis on the adverse effects of tamoxifen, particularly with regard to endometrial cancer and vascular-related toxic effects, which predominate in postmenopausal women. Recent reviews and individual studies of the relationship between tamoxifen and endometrial cancer indicate that the concern with regard to the level of excess risk of endometrial cancer may have been exaggerated and that, when endometrial cancers do occur in women who receive tamoxifen, they have as favorable a prognosis as those in women who do not receive the drug or who receive estrogen replacement therapy *(53–57)*.

In the P-1 trial, the average annual rate of invasive endometrial cancer in women 50 years of age or older who received tamoxifen was similar to what we had noted in the B-14 trial, i.e., about 2 per 1000 women per year. Of particular importance are the observations in this study that refute the claim that endometrial cancers occurring in tamoxifen-treated women are more aggressive, are less easily manageable, and cause more deaths than endometrial cancers that occur in non-tamoxifen-treated women or in those who have received hormone replacement therapy *(58)*. There is no evidence, either from this study or from any other NSABP trial *(59,60)*, to support those contentions. To date, all of the invasive endometrial cancers noted in the P-1 study in women who received tamoxifen were FIGO stage I, i.e., localized tumors. Thus, our findings fail to show that such tumors carry an unfavorable prognosis. Nonetheless, because of the increased risk of endometrial cancer, women receiving tamoxifen should have regular gynecologic examinations and should see their physicians if they experience abnormal vaginal bleeding.

Reports have appeared about the dangers of liver damage, hepatoma, colon cancer, and retinal toxicity resulting from tamoxifen administration. As the findings in this article and in reports from other NSABP studies attest, such concerns have not been substantiated. To date, no primary liver cancers have been reported in the P-1 trial and no increase in the incidence of either colon or any other second cancer, other than cancer of the uterus, has been observed. Also, no differences in the self-reporting of macular degeneration were observed (59 cases in the placebo group and 60 cases in the tamoxifen group). Reports suggesting that tamoxifen administration might be associated with ocular changes led to the conduct of a Tamoxifen Ophthalmic Evaluation Study in NSABP B-14. A recent report *(61)* from that study indicated that no cases of vision-threatening toxicity occurred among tamoxifen-treated women, although posterior subcapsular opacities were more frequently observed in that group. In this article, information is presented relative to the development of cataracts among women who were cataract free at the time of randomization. An increase in the rate of cataracts was found in the tamoxifen group. We do not consider the ophthalmic toxicities from tamoxifen administration sufficiently great to warrant withholding the drug from women such as those who participated in the P-1 trial.

Finally, as we *(10,62)* and others *(63,64)* have noted in previous investigations, certain vascular-related events reported in the P-1 study were more frequent in older women who received tamoxifen than in those who received placebo. While there was an overall increase in the average annual rate of stroke in women 50 years of age or older, uncertainty exists regarding the mechanism responsible for these results. There is also uncertainty regarding the cause of death in women who had a pulmonary embolism. Although three deaths were reported as being due to pulmonary embolism, all were associated with comorbid conditions that could have accounted for those deaths.

On the basis of the P-1 findings and this commentary, it is necessary to consider the question of who should receive tamoxifen to decrease their risk of breast cancer. The findings in this article indicate that women 50 years of age or younger who would have been eligible for the P-1 study are candidates for the drug. Similarly, women with a history of LCIS or atypical hyperplasia and postmenopausal women at high risk for breast cancer who have had a hysterectomy should be considered eligible for tamoxifen.

Women who have a history of DCIS may also be appropriate candidates for tamoxifen. Findings from other NSABP trials (B-17 and B-24) have demonstrated that the risk for an invasive breast cancer in women with localized DCIS is at least as high, if not higher, than that for women with a history of LCIS. In the current study, women in the placebo group who had a history of LCIS had an annual rate per thousand for breast cancer of 12.98. The annual rate of invasive cancer among women who underwent lumpectomy for DCIS was 23.7 (B-17) and, among those treated with lumpectomy and radiation therapy, it was 14.4 (B-24). In both of those studies, the risk of developing an invasive cancer was considerable. That risk could be substantially reduced by tamoxifen administration.

Another group of women who might also be candidates for tamoxifen are those at high risk for breast cancer because they carry BRCA1 or BRCA2 genetic mutations. In the P-1 study, blood that was obtained from participants for the conduct of future scientific investigations is now being used to determine how many of them had these mutations and whether tamoxifen decreased their breast cancer risk. While that information is, as yet, unavailable, offering women who carry these mutations the option of taking tamoxifen may be considered, since doing so provides an alternative to bilateral mastectomy.

Many women 50 years of age or older who have stopped menstruating, have not had a hysterectomy, and have no history of LCIS, DCIS, or atypical hyperplasia may also be eligible for tamoxifen. The decision relative to which of these women should or should not receive tamoxifen for breast cancer prevention is complex. The primary determinant for making such a decision relates to each woman's projected risk for breast cancer. The higher the risk, the more likely that tamoxifen would confer a benefit. Women whose breast cancer risk is sufficiently

high to offset the potential detrimental effects of tamoxifen would be candidates for the drug. However, women whose breast cancer risk is not as high should evaluate their individual benefits and risks with their physicians in order to make an informed decision with regard to the use of tamoxifen.

One way in which the benefit from tamoxifen can be estimated is to subtract the overall number of unfavorable events from the overall number of cancers prevented. Whether such a risk–benefit analysis is appropriate in deciding if tamoxifen should be used in the prevention setting is questionable. It seems inappropriate to view an endometrial cancer as being "equivalent" to a breast cancer, since, when endometrial cancers occur in women who receive tamoxifen, they are most often curable by hysterectomy and the mortality rate is minimal. Consequently, in the P-1 study, the breast cancers that would have occurred had tamoxifen not been used would have resulted in an estimated mortality rate that would likely have been higher than that observed from the undesirable effects of the drug. Moreover, the morbidity after hysterectomy would likely have been less than that resulting from the surgery, radiation, chemotherapy, and tamoxifen used to treat the unprevented breast cancer. Tools that can be used for determining a woman's breast cancer risk and the net effect from tamoxifen when used to prevent breast cancer are currently being developed.

As has been observed with the successive use of newer chemotherapeutic agents for the treatment of breast cancer, it is likely that new prevention agents will improve upon the benefits achieved with tamoxifen. The new NSABP chemoprevention trial P-2 represents such an effort. That trial will compare the toxicity, risks, and benefits of the selective ER modulator (SERM) raloxifene with those of tamoxifen. Raloxifene, which has been shown to prevent osteoporosis, will be evaluated in postmenopausal women to determine its value in preventing breast cancer without increasing the risk of endometrial cancer *(65)*.

The uncertainty of the clinical application of the current findings is analogous to uncertainties related to the use of systemic adjuvant therapy for breast cancer. With each demonstration of the worth of such therapy, questions continue to arise as to who should receive the treatment, i.e., who will benefit and who will not, who will not need the therapy because they will never demonstrate a treatment failure, how much of a benefit is worthwhile, and whether or not the toxicity and mortality encountered justify its administration. Despite these uncertainties, the use of adjuvant therapy was considered to be a major advance in the treatment of early stage breast cancer. The use of a chemopreventive agent denotes a similar advance in that it is being employed at an even earlier stage, i.e., during the origin and development of a phenotypically expressed cancer before its diagnosis.

Before submission of this article for publication, the results of two European studies were published *(66,67)* that failed to confirm the P-1 study findings. None of the information presented in them alters our conclusion that tamoxifen significantly reduces the probability of breast cancer in women at increased risk for the disease. The three studies are too dissimilar in design, population enrolled, and numerous other aspects to permit making valid comparisons among them. For a variety of reasons, it is unlikely that the European studies provided an adequate test of tamoxifen's effectiveness as a preventive agent. There were relatively few breast cancer events (70 in the British trial and 49 in the Italian study, as compared with 368 events in the P-1 study). It is likely that the paucity of events in the European studies was due to the relatively small number of participants and to the fact that the risk of breast cancer occurring among women in these trials was lower than that among participants in the P-1 trial. Because the criteria used for selecting participants in the Italian and the British studies were different from those used in the P-1 trial, women in those studies had a different risk for breast cancer than did P-1 trial participants, in that the expected proportion of ER-negative tumors could have been higher in them. This difference is important because tamoxifen is unlikely to prevent the occurrence of ER-negative tumors. The true statistical power of a study to detect an effect of tamoxifen would be a function of the number of tumors that are ER positive rather than a function of the total number of breast cancer events. Thus, if the expected proportion of ER-negative tumors is high, then the ability to show an effect of tamoxifen would be substantially reduced, since the statistical power that is based on the total number of events would be diminished. The fewer the number of events, the more likely it is that this reduction in statistical power is a critical factor affecting the ability to detect a difference between the study groups.

Noncompliance is another factor that affects the ability to detect differences, since it will result in a decrease of the anticipated effect of a drug. The rates of noncompliance were appreciable in the European trials. With small numbers of participants and relatively small numbers of events, as occurred in those trials, a high level of noncompliance will result in a substantial reduction in the likelihood of identifying a treatment effect. In the P-1 study, a high rate of noncompliance was used for sample-size estimates (10% per year of follow-up). Thus, the sample size was planned to be sufficiently large to preserve adequate power even in the presence of a high rate of noncompliance.

Perhaps the most important reason for the failure of the European studies to provide an adequate test of tamoxifen's effect could be due to the fact that 41% of the women in the British trial and 14% in the Italian study received hormone replacement therapy. This introduced a potential confounding factor that could have interfered with testing of the hypothesis that gave rise to the conduct of both trials. The use of hormone replacement therapy was considered to be a protocol violation in the P-1 trial. Until a clinical trial evaluating the efficacy of using tamoxifen with hormone replacement therapy is conducted, it is difficult to assess the relevance of findings from trials using that regimen.

The issue has been raised that the P-1 trial was stopped prematurely and that the findings were reported too early. The trial was stopped only when the independent monitoring committee for that study (ERSMAC), on the basis of stopping rules established before the onset of the trial, concluded that the primary study hypothesis had been confirmed beyond a reasonable doubt, i.e., that tamoxifen decreased the incidence rate of invasive breast cancer ($P<.00001$). It was concluded that additional follow-up would not have resulted in improved estimates of treatment effects that would have justified withholding from the participants on placebo the knowledge that tamoxifen was an effective prophylactic agent. This allows those women on placebo to consider taking tamoxifen. While additional studies are needed to address the issues that have arisen as a result of our findings, we consider it highly inappropriate to not offer tamoxifen to women who are similar to those in the P-1 study and who may benefit from its use as a breast cancer preventive agent.

Appendix A. Clinical centers participating*

Name of center	Principal investigator	Program coordinator
Albert Einstein Cancer Center, Philadelphia, PA	A. Desai	E. Barksdale
Allegheny Cancer Center Network, Pittsburgh, PA	N. Wolmark	D. Gosik
Alliant Health System, Louisville, KY	J. Hamm	B. MacCracken
Arizona Cancer Center, Tucson	D. Alberts	H. Fritz
Arrington Cancer Research and Treatment Center, Lubbock, TX	C. Geyer, Jr.	P. Hagan-Jones
Atlanta Breast Cancer Prevention Program	J. Lesesne	R. Hallett
Atlanta Community Women's Health Project, GA	F. Brescia	C. Shulman
Atlanta Regional CCOP	C. Austin	P. Remke
Baltimore Clinical Center, MD	G. Elias	S. Honts
Baptist Cancer Institute CCOP, Memphis, TN	L. Schwartzberg	T. Stewart
Baptist Health System, Birmingham, AL	T. Gaskin III	K. Hawkins
Baptist Regional Cancer Institute, Jacksonville	N. Abramson	P. Stokes
Bassett Hospital, Cooperstown, NY	A. Nafziger	L. Stragand
Bay Area Cancer Control Consortium, CA	J. Luce	M. Milian-Menendez
Baylor-Sammons Cancer Center, Dallas, TX	M. Grant	B. Quast
Boston University Medical Center, MA	M. Prout	L. Pottier
Breast Health Center, New England Medical Center, Boston, MA	R. Graham	C. Mullen
British Columbia Cancer Agency, Vancouver	U. Kuusk	L. Fearn
Carle Cancer Center CCOP, Urbana, IL	A. Hatfield	L. Foster
Cedar Rapids Oncology Project CCOP, IA	K. Wright	P. Brockschink
Central Illinois CCOP, Springfield	J. Wade	S. Shonkwiler
Central New York Group, Syracuse	J. Kirshner	K. Shedlock
Charleston/Morgantown Groups, WV	S. Jubelirer	E. Javins
City of Hope, Duarte, CA	L. Wagman	D. Hooks
Colorado Cancer Research Program CCOP, Denver	P. Raich	C. McElfatrick
Columbia River CCOP, Portland, OR	K. Lanier	L. Birenbaum
Columbus CCOP, OH	L. Laufman	S. Oxley
Connecticut Task Force, Hartford	P. DeFusco	J. Kulko
Credit Valley Hospital, Mississauga, ON	R. Myers	S. Neville
Creighton Cancer Center, Omaha, NE	J. Mailliard	C. Reed
Cross Cancer Institute, Edmonton, AB	A. Lees	C. Danbrook
Dana-Farber Consortium, Boston, MA	J. Garber	B. Cahoon
Dartmouth-Hitchcock Medical Center, Lebanon, NH	J. Ross	J. Strohbehn
Dayton Clinical Oncology CCOP, OH	H. Gross	E. Craddick
Duke University Medical Center, Durham, NC	L. Sutton	K. Warren
Duluth CCOP, MN	R Dalton	D. Swan
E. Carolina University, Greenville, NC	D. Lannin	M. Edwards
E. Maine Medical Center, Bangor	P. Brooks	A. Hayes-Crosby
Ellis Fischel Cancer Center, University of Missouri, Columbia	S. Standiford	T. Schulte
Fairfax Hospital, Falls Church, VA	N. Robert	M. Dittberner
Fox Chase Cancer Center, Philadelphia, PA	M. Daly	J. James
Geisinger Breast Clinic of Danville, PA	J. Evans	M. Lamey
Georgetown University Lombardi Cancer Center, Washington, DC	C. Isaacs	J. Dritschilo
Glens Falls Hospital Cancer Program, NY	D. Mastrianni	P. Maksymik
Greater Phoenix CCOP, AZ	D. King	P. Wade
Greenville CCOP, SC	J. Giguere	J. Martin
Hamilton Regional Cancer Center, ON	A. Arnold	S. Holohan
Harbor-UCLA, Torrance, CA	R. Chlebowski	V. Marsoobian
Hennepin County Medical Center, Minneapolis, MN	R. Zera	L. Tatro
Hoosier Oncology Group, Indianapolis, IN	P. Loehrer	F. Monaco
Huntsman Cancer Institute, Salt Lake City, UT	J. Ward	C. Walker
Illinois Cancer Center, Chicago, IL	A. Benson III	S. French
Illinois Masonic Cancer Center, Chicago	S. Taylor	P. Wellmann
Jewish General/St. Mary's Montreal, PQ	R. Margolese	N. Warrington
Kaiser Permanente CCOP, San Diego, CA	J. Polikoff	M. Wolgast
Lehigh Valley Hospital, Allentown, PA	M. Gittleman	E. Ladd
Long Beach Memorial Cancer Institute, CA	C. Forsthoff	F. Magy
Los Angeles Oncologic Institute, CA	C. Presant	M. Aldana
M. D. Anderson Cancer Center, Houston, TX	D. Booser	D. Weber
M. D. Anderson Cancer Network, Ft. Worth, TX	V. Stark-Vancs	E. Fisher
Main Line Health System CCOP, Wynnewood, PA	T. Frazier	L. O'Neill
Manitoba Cancer Foundation, Winnipeg, MB	D. Bowman	K. McDonald
Marshfield Clinic CCOP, WI	J. Hoehn	N. Goldberg
Mayo Clinic CCOP, Scottsdale, AZ	R. Wheeler	B. Roedig
Medical Center of Delaware CCOP, Wilmington	T. Wozniak	A. Steele
Medical College of Virginia MBCCOP, Richmond	C. Desch	G. Parker
Memorial Sloan-Kettering Cancer Center, New York, NY	A. Heerdt	R. Gross

Appendix A (continued). Clinical centers participating*

Name of center	Principal investigator	Program coordinator
Mercy Hospital CCOP, Scranton, PA	M. Hyzinski	V. Pauli
Metro-Minnesota Center, St. Louis Park	P. Flynn	A. Deshler
Midwest BCPT, Kansas City, MO	J. Paradelo	M. Goodpaster
Milwaukee Group, WI	W. Donegan	J. Jensen
Montana Group, Billings	D. Myers	S. Hall
Michigan State University, East Lansing, MI	N. Dimitrov	C. Robins
N.E. Ohio BCPT Group, Cleveland	R. Bornstein	L. Mamounas
New York Consortium: St. Vincent's Hospital/Guttman	M. Wallack	M. Montegari
N. New Jersey CCOP, Hackensack	R. Rosenbluth	J. Behr
N. Shore University Hospital CCOP, Manhasset, NY	L. Weiselberg	D. Mayberry
N.W./Virginia Mason CCOP, Tacoma, WA	I. Pierce	K. Hart
Ochsner CCOP, New Orleans, LA	C. Kardinal	M. Bateman
Ohio State/James Cancer Hospital, Columbus	W. Farrar	J. Bennett
Oklahoma City Consortium, OK	K. Boatman	M. Watson
Project for Prevention of Cancer, Sein, PQ	L. Deschenes	A. Christen
Puget Sound Oncology Consortium, Seattle, WA	R. Clarfeld	J. Machia
Roswell Park Cancer Institute, Buffalo, NY	S. Edge	P. Burke
Royal Victoria Hospital, Montreal, PQ	H. Shibata	R. Santos
Rush-Presbyterian-St. Luke Medical Center, Chicago, IL	J. Wolter	M. Escobar
S. Florida Group, Miami Beach	E. Davila	F. Cenciarelli
S. Nevada CCOP, Las Vegas	J. Ellerton	K. VanWagenen
San Joaquin Valley CGOP, Fresno, CA	R. Farah	J. Atchley
San Juan MBCCOP, Puerto Rico	W. Cáceres	D. Cuadrado
Scott & White Texas A&M, Temple, TX	K. Kimmey	E. Lagow
Sioux Community Cancer Consortium CCOP, Sioux Falls, SD	L. Tschetter	J. Norman
Southeast Cancer Control Consortium CCOP, Winston-Salem, NC	J. Atkins	R. Burgess
St. Francis Program CCOP, Tulsa, OK	G. Schnetzer III	S. Segler
St. Louis-Cape Girardeau CCOP, MO	A. Greco, Jr.	C. Antinora
St. Luke's Hospitals, CCOP, Fargo, ND	R. Levitt	D. Pilon
St. Mary/Long Beach Community, CA	S. Tchekmedyian	D. Jackson
Stanford University, Palo Alto, CA	R. Carlson	C. Schurman
Strang Cancer Prevention Center, New York, NY	M. Osborne	R. Weiss
Sutter/California Healthcare System Center, Sacramento, CA	V. Caggiano	L. Ayer-Rand
Texas Tech. University Health Sciences Center, Southwest Cancer Center, Lubbock	E. Cobos	S. Dixon
Thompson Cancer Center, Knoxville, TN	T. Panella	J. Rodgers
Toledo CCOP, OH	P. Schaefer	D. Frie
Tom Baker Cancer Centre, Calgary, AB	A. Paterson	A. Hades
Toronto Hospital Breast Group, ON	P. Goss	J. Smith
University of Alabama at Birmingham	J. Carpenter, Jr.	L. Crosby
University of Arkansas for Medical Science, Little Rock	S. Klimberg	M. Colvert
University of California–Davis Cancer Center, Sacramento	J. Goodnight, Jr.	L. Clawson
University of California–Los Angeles Center for Health Sciences	P. Ganz	B. Kahn
University of Chicago, IL	R. Arenas	B. Bulliner
University of Cincinnati Medical Center, OH	B. Aron	
University of Hawaii, Honolulu	R. Oishi	A. Kelminski
University of Iowa, Iowa City	P. Jochimsen	M. Spaight
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University of Montreal, PQ	A. Robidoux	L. Robitaille
University of North Carolina, Chapel Hill	S. Bernard	B. Kaluzny
University of New Mexico Cancer Center, Albuquerque	A. Mangalik	A. Parsons
University of Pennsylvania Cancer Center, Philadelphia	M. Torosian	P. O'Neill
University of South Alabama MBCCOP, Mobile	M. Conrad	M. Grove
University of Texas Health Science Center, San Antonio	A. Cruz	I. Presas
University of Wisconsin Comprehensive Cancer Center, Madison	J. Stewart	T. Fass
Upstate Carolina CCOP, Spartanburg, SC	R. Sticca	K. Queen
USC/Norris Comprehensive Cancer Center, Los Angeles, CA	D. Spicer	E. Sales
Vermont Cancer Center/University of Vermont, Burlington	D. Krag	S. Dion
W. Pennsylvania Project, Pittsburgh, PA	V. Vogel III	L. Robertson
Wayne State University, Detroit, MI	M. Simon	C. Kresge
Wichita CCOP, KS	H. Hynes	M. Good
Wilford Hall Medical Center, TX	S. Wilks	B. Chaparro
Women's College Hospital, Toronto, ON	L. Lickley	M. Oldfield

*CCOP = Community Clinical Oncology Program; MBCCOP = Minority-Based Community Clinical Oncology Program; CGOP = Cooperative Group Outreach Program.

Appendix B. The following key personnel were involved in the planning, implementation, conduct, and analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT)

BCPT Steering Committee

Jeffrey Abrams	Nikolay V. Dimitrov	Charles Geyer, Jr.	Joan James	Richard Margolese	D. Lawrence Wickerham
Nancy Brinker	Bernard Fisher	Andrew Glass	C. Conrad Johnston, Jr.	Carol Redmond	H. Samuel Wieand
Susan Braun	John Flack	William Harlan	Carl Kardinal	Andre Robidoux	Norman Wolmark
Walter Cronin	Leslie Ford	Elizabeth Hart	Maureen Kavanah	Phillip Stott	
Mary Daly	Patricia Ganz	Brian Henderson	Joan McGowan	Victor Vogel	

Endpoint Review, Safety Monitoring, and Advisory Committee (ERSMAC)

Martin Abeloff	Theodore Colton	Laurence Freedman	Barbara Hulka	Elliot Rapaport	Barbara Tilley
Michele Carter	Polly Feigl	Lawrence Friedman	Howard Judd	Carol Redmond	

Participant Advisory Board

Elsie Anderson	Barbara Capuzelo	Elizabeth Lee	Beverly Munn	Marty Smith	Helene Wilson
Judith Bingham	Mary Ellen Gorman	Titas Marquez	Rici Rutkoff	Romenza Kaye Thomas	
Karen Brennan	Sandra Kanicki	Jeannie Morice	Mary Sankolewicz	Lonnie Williams	

BCPT Coordinator Committee

Robin Burgess	Joan James	Joelle Machia	Gwendolyn Parker	Barbara Simonick	Marilyn Zack
Anita Hades	Elisabeth Ladd	Mary Pat Matisko	Crystal Rabbas	Connie Szczepanek	
Donna Jackson	Deborah Lifsey	Nancy Morton	Sidney Shonkwiler	Diane Weber	

Osteoporosis Committee

Stewart Anderson	Sol Epstein	Carl Kardinal	Robert Lindsay	Joan McGowan	Janet Wolter
Alan Burshell	C. Conrad Johnston, Jr.				

Quality of Life Committee

David Cella	Patricia Ganz	Elizabeth Maunsell	A. H. G. Paterson	Harvey Schipper	Victor Vogel
Walter Cronin	Jean-Clause Lasry	Carol Moinpour	Wendy Schain	Sally Schumaker	John Ware, Jr.
Richard Day					

Gynecology Committee

Joseph Costantino	Charles Geyer, Jr.	Lawrence Levy	Carolyn Runowicz	D. Lawrence Wickerham	H. Samuel Wieand
Mary Daly	Maureen Kavanah	George Lewis, Jr.			

Recruitment, Promotion, and Compliance Committee

Erwin Bettinghaus	Paul Engstrom, Jr.	Mary Ketner	Rose Mary Padberg	Sherrie Reynolds	Rodger Winn
Cathy Coleman	Leslie Ford	Amy Langer	Lori Psillidis	Edmund Ricci	Antronette Yancey
Joseph Costantino	V. Craig Jordan				

Cardiovascular Committee

Joseph Costantino	William Harian	Santica Marcovina	Russell Tracy	D. Lawrence Wickerham	H. Samuel Wieand
John Flack	Lewis Kuller	Steven Reis			

Northwest Lipid Research Laboratories

Santica Marcovina	Tess McMillan	Katherine Rosecrans	Tricia Speer	

Epicare Center

Farida Rautaharju	Pentti Rautaharju

Advisors/Consultants

Zora Brown	Joyce Cramer	Michael Gorin	Pat Halpin Murphy	Mary-Claire King	Steven Reis
Les Butler					

National Cancer Institute (NCI)

Kathy Crosson	Jennifer Flach	Karen Johnson	Susan Nayfield	Jackie McNulty	Donna Shriner
Barbara Dunn	Leslie Ford	Sunita Kallarakal	Eleanor Nealon	Rose Mary Padberg	Kara Smigel
Alfred Fallavollita	Peter Greenwald	Richard Klausner	Barnett S. Kramer	Judy Patt	Crystal Wolfrey

NSABP Biostatistical Center

Lynne Anderson	Joseph Costantino	Arthur DeCillis	Lynn Holman	Darlene Kiniry	Michele Randolph
Stewart Anderson	Walter Cronin	Kenneth Duff	Regina Hopkins	Paul Magee	Carol Redmond
Gordon Bass	Deborah Darnbrough	Janet Famiglietti	Michael Hritz	Mary Passarello	H. Samuel Wieand
Wayne Baughman	Richard Day				

NSABP Operations Center

Jennifer Aikin	Bernard Fisher	Jacek Kopek	Colleen Meyers	Lori Psillidis	D. Lawrence Wickerham
Jill Bowlus	Gladys Hurst	Terry Mamounas	Joyce Mull	Donna Szczepankowski	Amy Wolenski
Lora Ann Bray	Mary Ketner	Mary Pat Matisko	Debra Pollak	Elizabeth Tan-Chiu	Norman Wolmark
Joan Dash					

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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APPENDIX

b. Abstracts from 19th Annual Meeting of Society for Clinical Trials

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DEMOGRAPHIC CHARACTERISTICS AND QUALITY OF LIFE FACTORS AMONG THE PARTICIPANTS OF THE BREAST CANCER PREVENTION TRIAL

Joseph P. Costantino, Richard Day, Walter Cronin, D. Lawrence Wickerham, Bernard Fisher, Carol Redmond, Maureen Kavanah and Norman Wolmark for the National Surgical Adjuvant Breast and Bowel Projects
University of Pittsburgh
Pittsburgh, Pennsylvania

The Breast Cancer Prevention Trial (BCPT) completed accrual on September 30, 1997. A total of 13, 388 women have been randomized to receive 20 mg per day of tamoxifen or placebo for five years. The trial is still ongoing and the results of the study can not be reported until follow-up is completed. However, now that accrual is finished, a full description of the participant population can be provided. This type of information is of interest as it would provide some insight into the type of population that would volunteer for cancer prevention trials and could be useful for the development of recruitment strategies for future studies. In addition to demographic characteristics and information regarding breast cancer risk factors, baseline data was collected regarding the participants' quality of life parameters. The data concerning quality of life represents one of the largest single sources of such information among healthy women in North America.

Generally speaking, the women who volunteered to participate in the trial represent middle to upper middle-class women who work outside the home. Methods used for recruitment will be summarized and the yield for each method will be described. Details regarding the distributions by age, race, education, occupation, income, factors related to breast cancer risk, medical history and aspects of quality of life will be presented. Quality of life aspects include measures of physical and mental performance obtained from the SF-36 instrument. Differences in quality of life aspects noted by age, education, estimates of breast cancer risk and other factors will be described.

40
SENSITIVITY ANALYSES OF Q-TWIST MODEL FOR INTERFERON MAINTENANCE THERAPY IN MULTIPLE MYELOMA

Tong Li, Benny Zee, Keith James and Michael Brundage
National Cancer Institute of Canada Clinical Trials Group
Kingston, Ontario, Canada

A quality-adjusted time without symptoms and toxicity analysis (Q-TWiST) was conducted by NCIC CTG to assess the trade-off between the benefits of interferon (IFN) maintenance therapy and toxicities in patients with multiple myeloma. The purpose of this paper is to propose methodologies for assessing various assumptions in Q-TWiST model by conducting sensitivity analyses. The Q-TWiST model was used to compare the two treatment arms based on the following three health states: Tox - time with interferon toxicity; TWiST - time without disease relapse and toxicity; Rel - time after relapse. In the original Q-TWiST analysis, Tox was defined as time with moderate or worse toxicity. To assess the impact of Tox definition, Q-TWiST was calculated by defining Tox as: 1) time with grade 3 or worse toxicity; and 2) time with any grade of toxicity (i.e., grade 1 or worse). Also, a Q-TWiST result derived from including an "other toxicities" item into the toxicity health state was considered. In order to determine the impact of certain extreme covariate patterns, a proportional hazards Q-TWiST model was used to evaluate the outcome. The results show that there is a significant benefit in favour of IFN if patients are more willing to tolerate IFN toxicity. The benefit is obvious when only severe toxicity is being included in the Tox health state. IFN remains to be better for most of the utility functions even when only grade 1 or worse toxicities were considered in the Tox health state. In addition, the result is similar

58
REASONS FOR ENROLLMENT AND CONTINUED PARTICIPATION IN A LONGITUDINAL, OBSERVATIONAL STUDY: THE INTERSTITIAL CYSTITIS DATA BASE (ICDB) STUDY EXPERIENCE

Yvonne Matthews-Cook, J. Richard Landis, Marilou Foy, John Kusek, Leroy Nyberg and the ICDB Study Group
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Several studies have evaluated the factors which motivate people to enroll in comparative clinical trials. Little is known, however, about what motivates people to join an observational study which does not offer a prescribed treatment regimen.

Interstitial cystitis (IC) is a chronic bladder disease characterized by increased voiding frequency, nocturia, urgency, and pain. The ICDB Study is a prospective, observational study designed to characterize the treated course of IC. At the final study visit, participants were asked to complete an Opinion Survey, modified from Mattson et al (Controlled Clinical Trials 6:156 (1985), which looked at issues of enrollment and continued participation. Of the 369 participants (90.7% female) who have completed the final study visit, 364 (99%) completed the survey.

The most frequent reasons reported for enrolling were to learn more about IC (96%) and IC treatments (95.4%) help others with IC (85.8%) and take part in research (85%). The primary reasons for continued participation were to help find a cure for IC (97.4%), further the general knowledge of IC (95.9%), take part in research (86%), and help others (85%).

The most frequently reported problems with participating included traveling to and from the clinic (24.4%), parking (20.1%), and clinic location (18.2%). However, 87.2% indicated they would volunteer for a future study like the ICDB and 93.2% would recommend such a study to others.

We conclude that patients who joined the ICDB Study were moved to enroll and continue participation by an interest to learn more about IC and IC treatments and to help others with IC.

(This work is supported by NIH U01 DK45021.)

59
ELECTRONIC MONITORING OF PARTICIPANT ADHERENCE IN THE NSABP BREAST CANCER PREVENTION TRIAL (BCPT)

Richard Day, David F. Cella, Patricia Ganz and Joseph P. Costantino
University of Pittsburgh
Pittsburgh, Pennsylvania

Participant adherence in the NSABP BCPT is routinely carried out using pill counts and nursing staff assessments based on participant reports. In addition, 100 women enrolled in the BCPT at four collaborating centers (Rush-Presbyterian, Chicago; University of California, Los Angeles; Fox Chase Cancer Center, Philadelphia; Georgetown University Medical Center, Philadelphia; Georgetown University Medical Center, Washington, D.C.) were monitored at the 3, 6, and 12 month points in the trial using the APREX Corporation's electronic Medication Event Monitoring System (MEMS), which records the number, date and time of pill bottle openings using a microchip contained in the bottle cap.

This paper analyzes the results of this study and assesses the usefulness of including electronic monitoring with other types of adherence measures in large-scale prevention trials. Results will be presented comparing estimated levels of adherence recorded by the three recording systems (MEMS, pill count, and staff estimate) using a weighted kappa statistic. Overall kappas for the comparison of MEMS to pill counts for the three time points vary between 0.28 to 0.36. For the comparison of MEMS to staff assessed compliance overall

APPENDIX

c. Slides from Presentations at 19th Annual Meeting of Society for Clinical Trials

Preliminary Analysis of Quality of Life Data from the NSABP Breast Cancer Prevention Trial (BCPT)

Richard Day, Ph.D.
Joseph P. Costantino, Ph.D.
University of Pittsburgh

Patricia Ganz, M.D.
University of California at Los Angeles

May 1998

Cohort selected for presentation:

11064 women randomized to the BCPT over the first 24 months of the study.

Follow-Up period selected for presentation:

Baseline examination and first 36 months of follow-up data (3, 6,12, 18, 24, and 36 mo. exams)

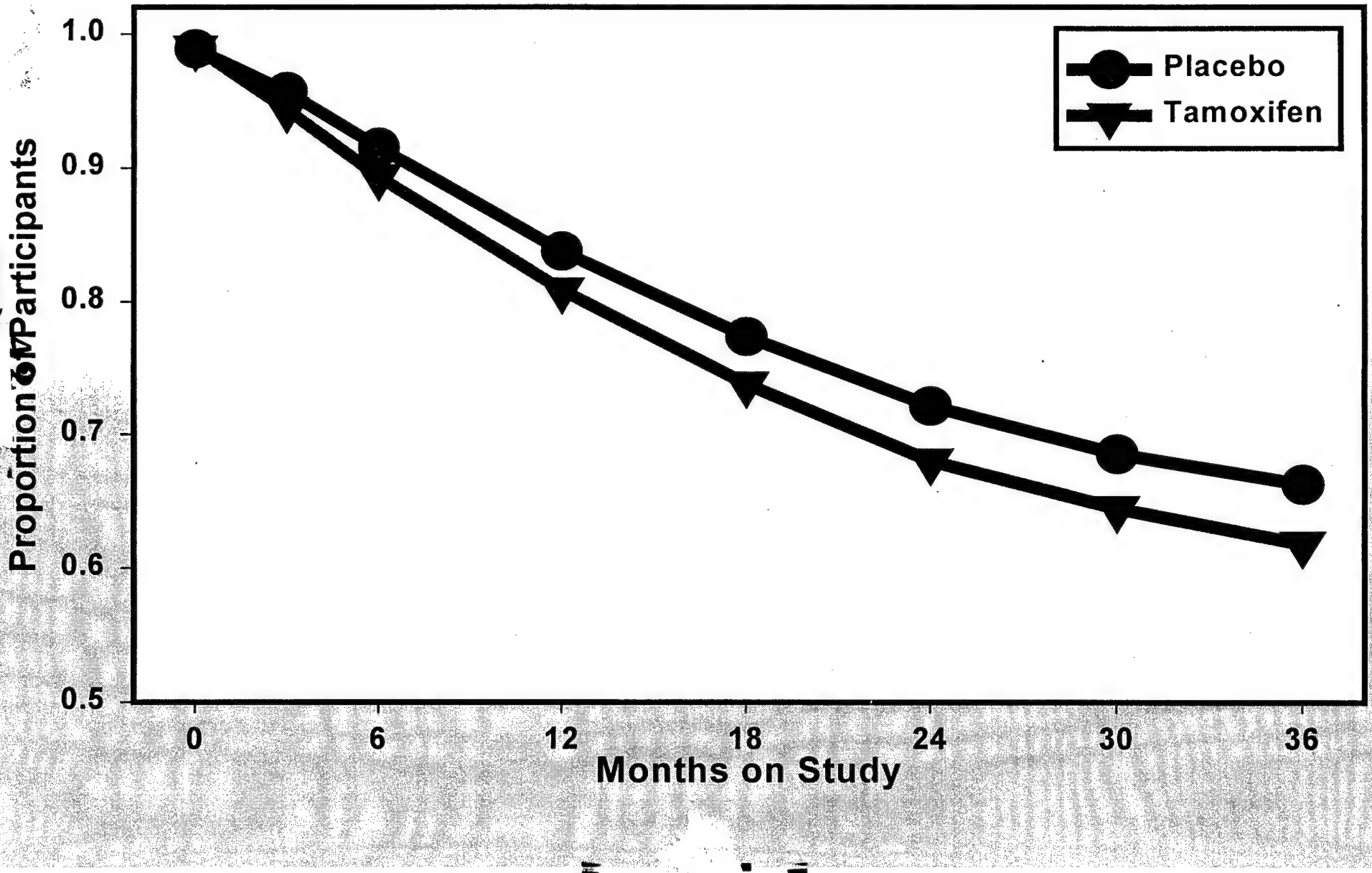
Treatment Characteristics of 11064 BCPT Participants

Treatment	Age Groups 35-49 yrs.	50-59 yrs.	≥60 yrs.	Overall
Placebo	2182 (39.4%)	1695 (30.6%)	1660 (30.0%)	5,537 (50.05%)
Tamoxifen	2179 (39.4%)	1700 (30.8%)	1648 (29.8%)	5,527 (49.95%)
Total	4361 (39.4%)	3395 (30.7%)	3308 (29.9%)	11,064 (100%)

Risk Characteristics of 11064 BCPT Participants

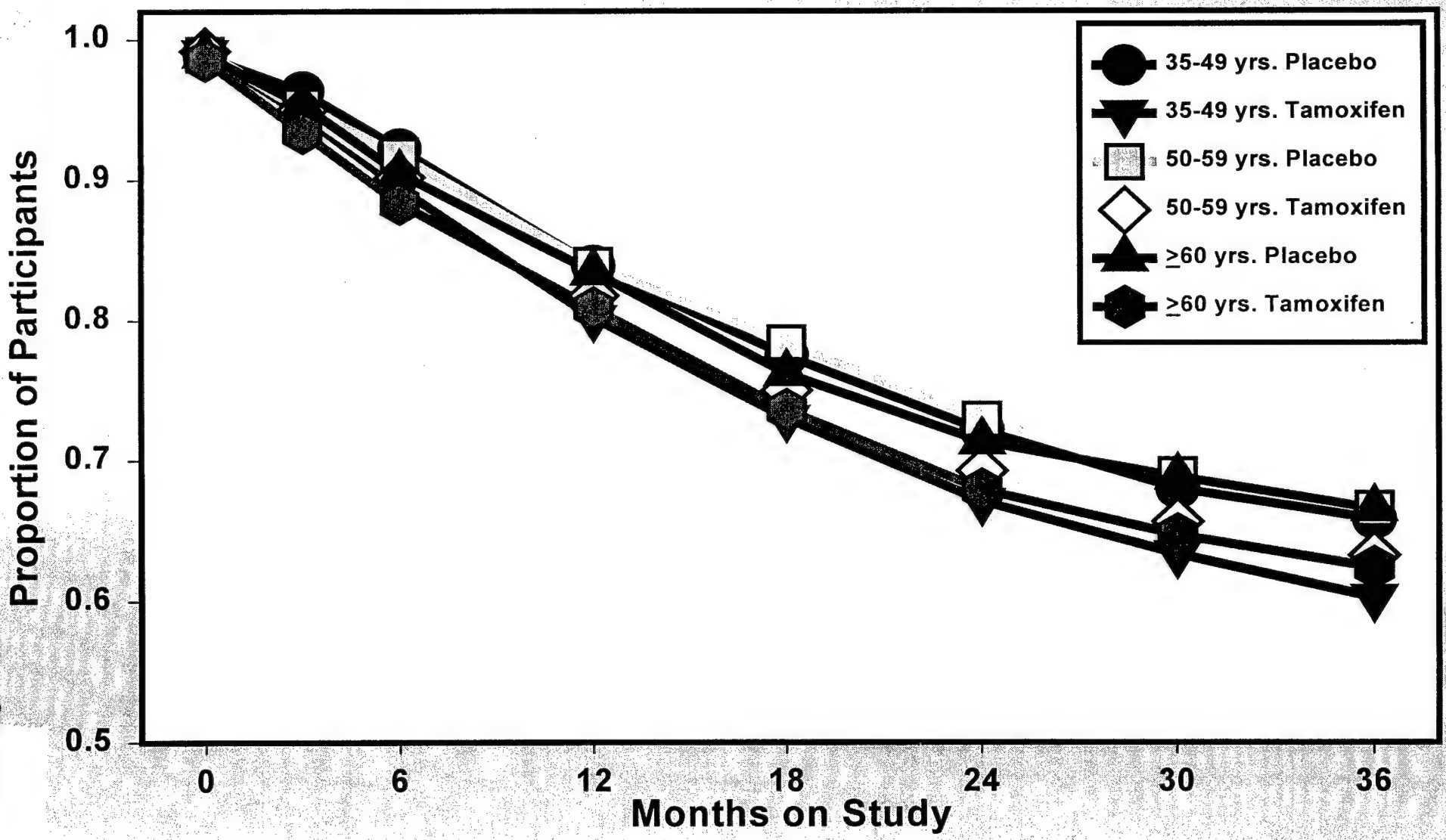
Relative Risk	Age Groups 35-49 yrs.	50-59 yrs.	≥60 yrs	Overall
Mean RR	6.93	5.10	3.73	5.41
SE	0.06	0.06	0.05	0.04
Median	5.39	3.59	3.03	4.23

Treatment Adherence for BCPT Participants by Arm and Examination



TA1

Treatment Adherence for BCPT Participants by Arm, Age Group and Examination

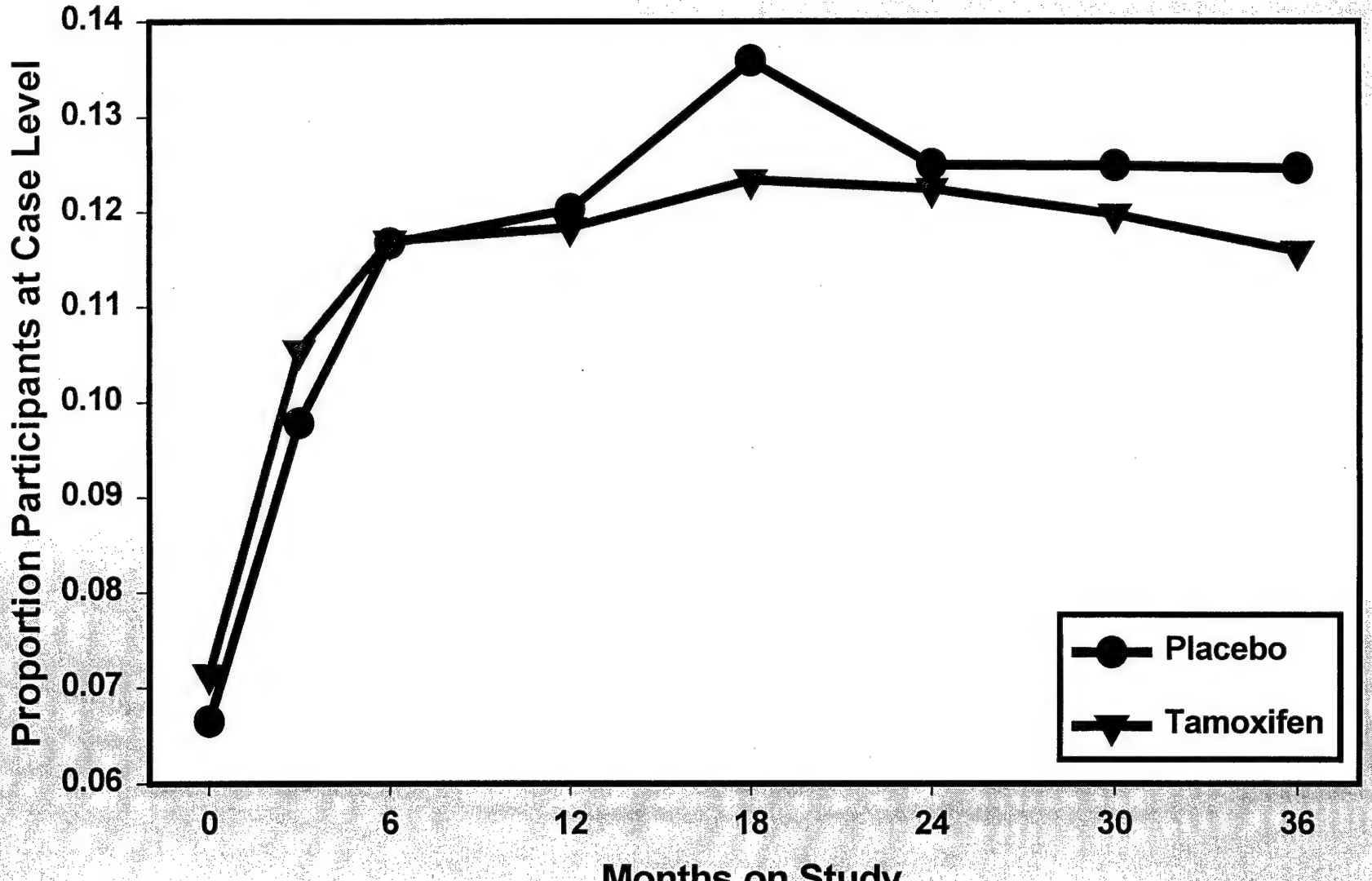


TA2

Components of the BCPT Quality of Life Questionnaire (104 Items)

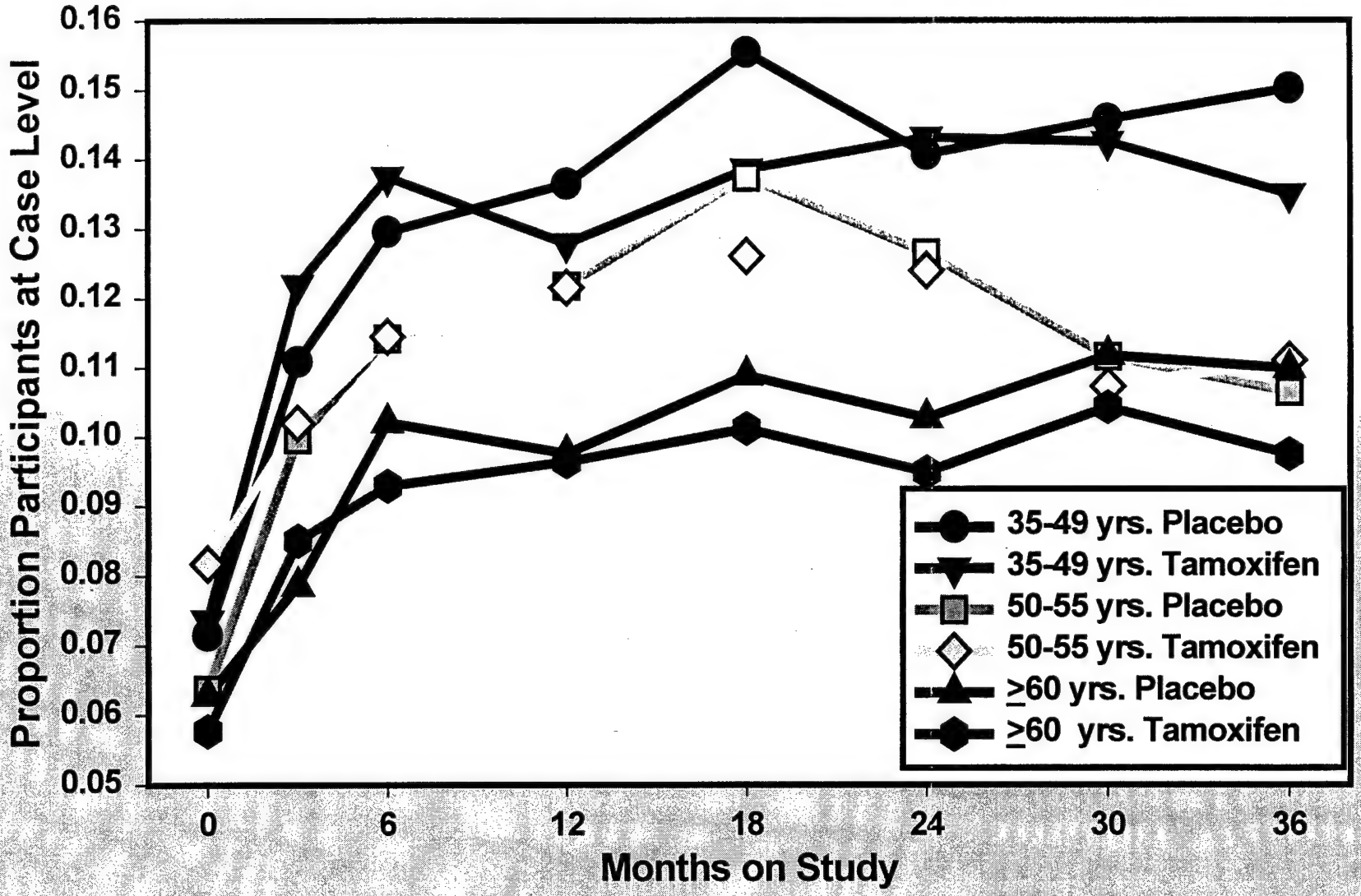
- Center for Epidemiological Studies-Depression Scale (CES-D, 20 Items)
- Symptom Checklist (43 Items)
- Medical Outcomes Study - Short Form (SF-36, 36 Items)
- Medical Outcomes Study - Sexual Functioning Scale (5 Items)

Proportion of BCPT Participants with CES-D Scores at the Level of a Potential Case (≥16) by Arm and Examination



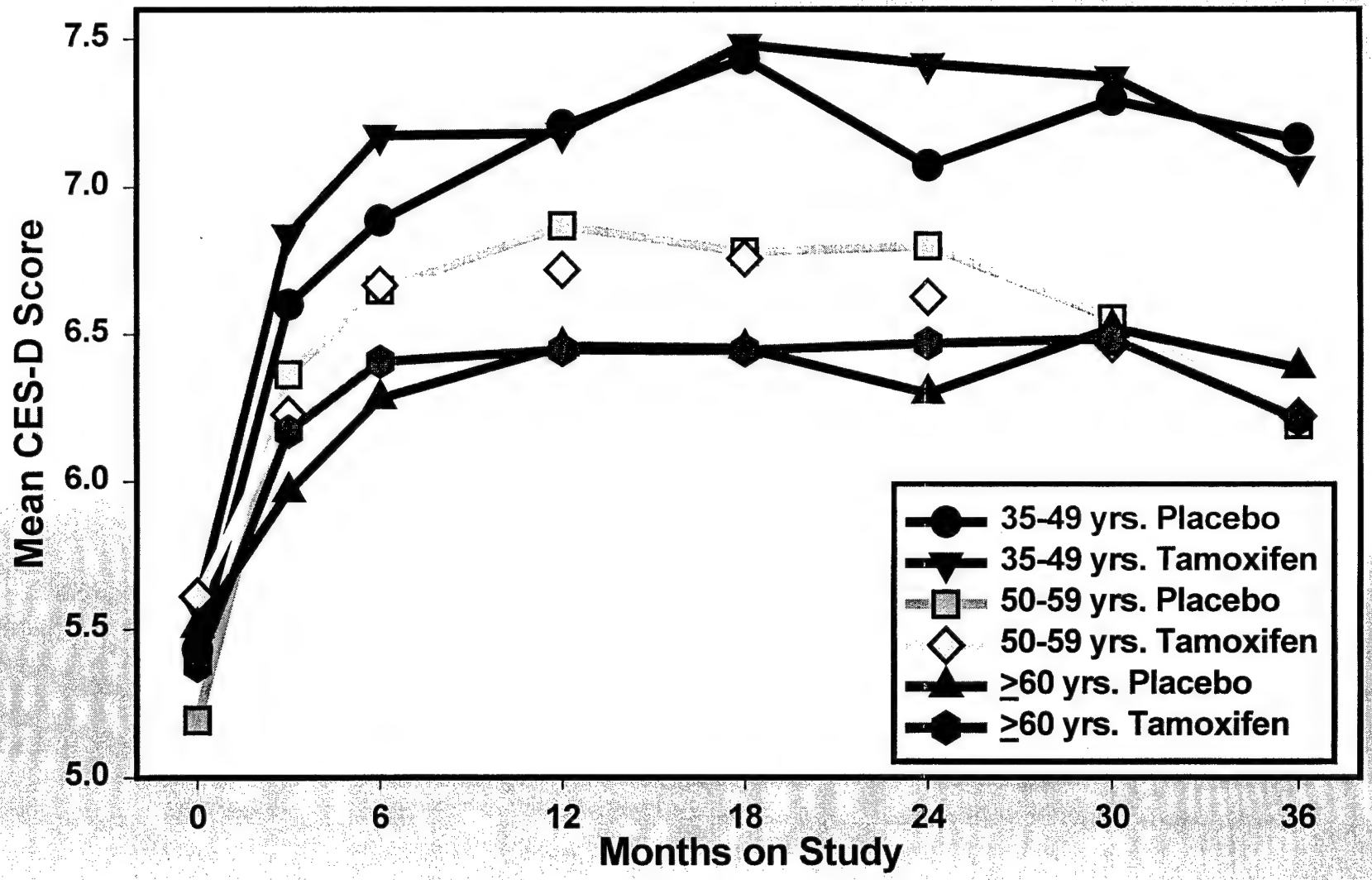
CESD1 30/4/98

Proportion of BCPT Participants with CES-D Scores at the Level of a Potential Case (≥16) by Arm, Age Group and Examination



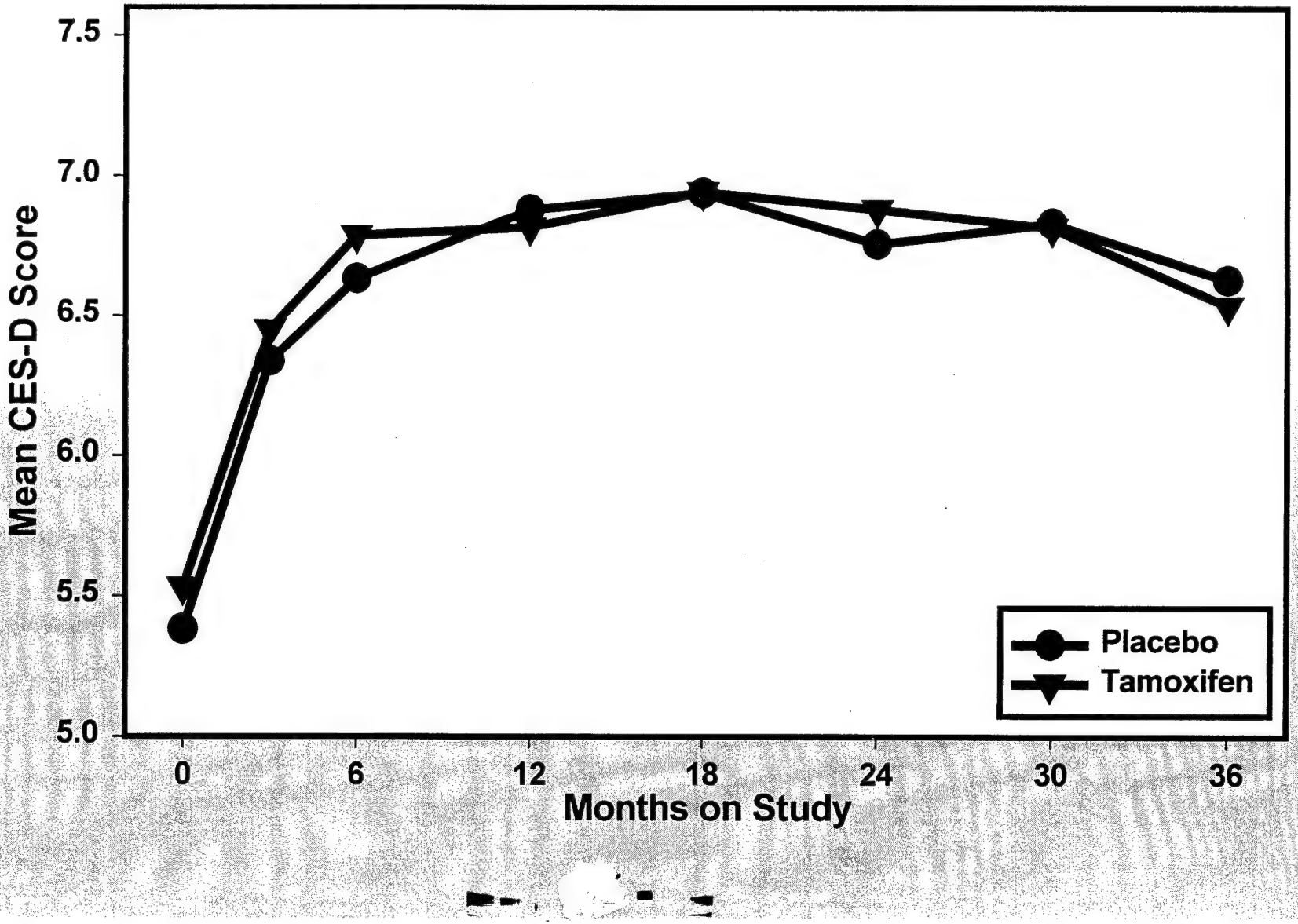
CESD2 30/4/98

Mean CES-D Score for BCPT Participants by Age Group, Arm and Examination



CESD3 30/4/98

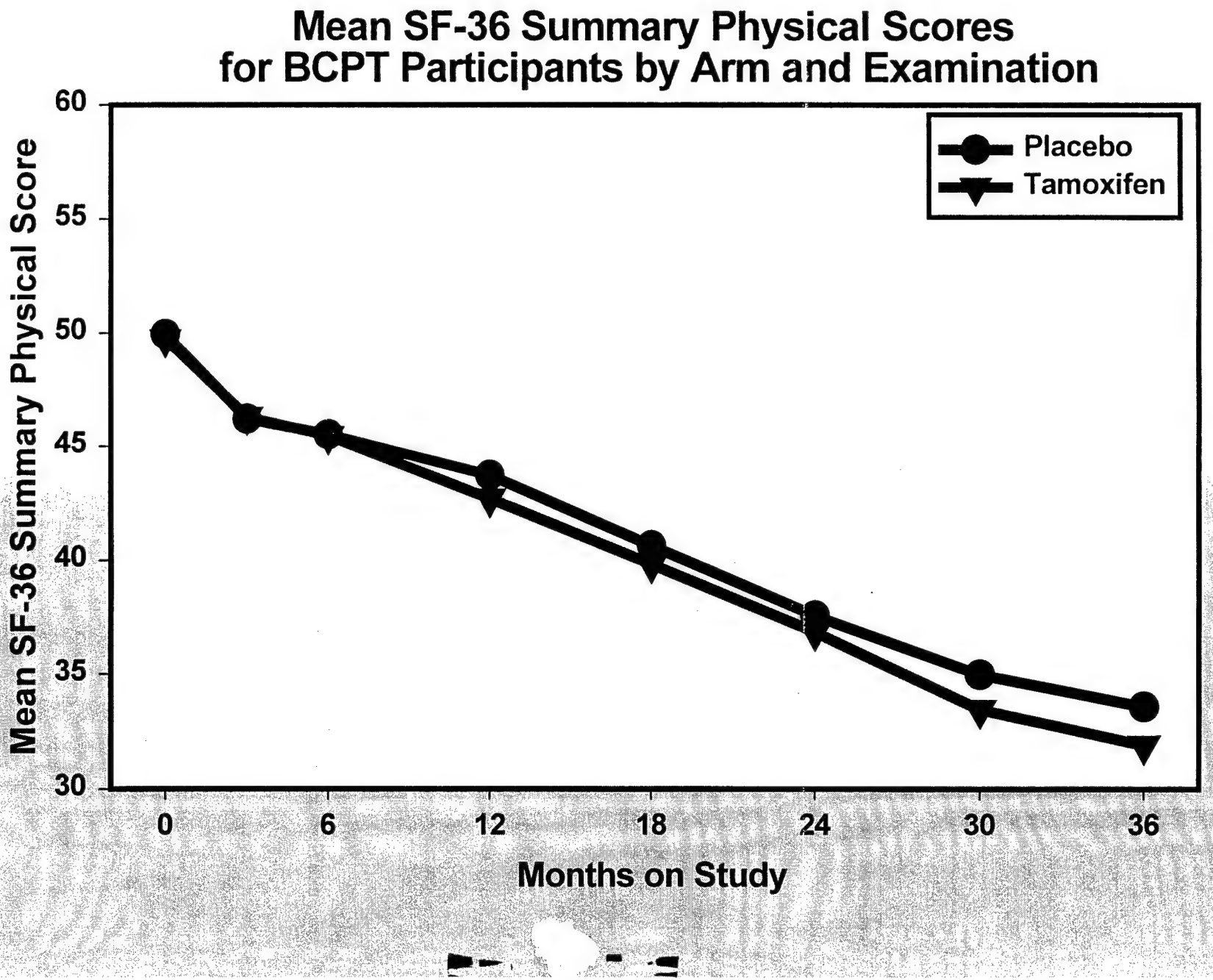
Mean CES-D Score for BCPT Participants by Arm and Examination



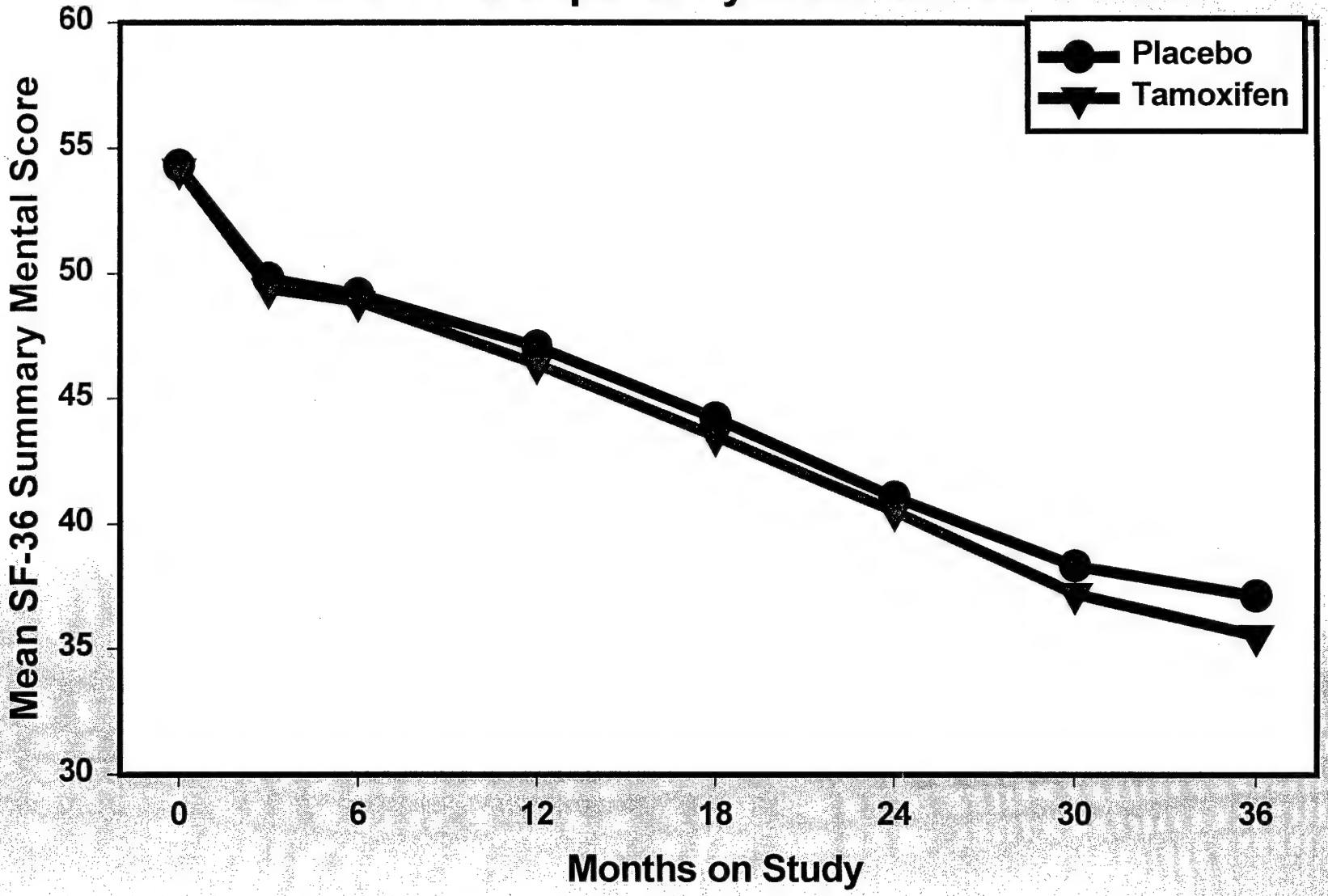
CESD4 30/4/98

SF-36 SCORING

SF-36 Scales	SF-36 Summary Measures
Physical Functioning Role-Physical Bodily Pain General Health	Physical Health
Vitality Social Functioning Role-Emotional Mental Health	Mental Health

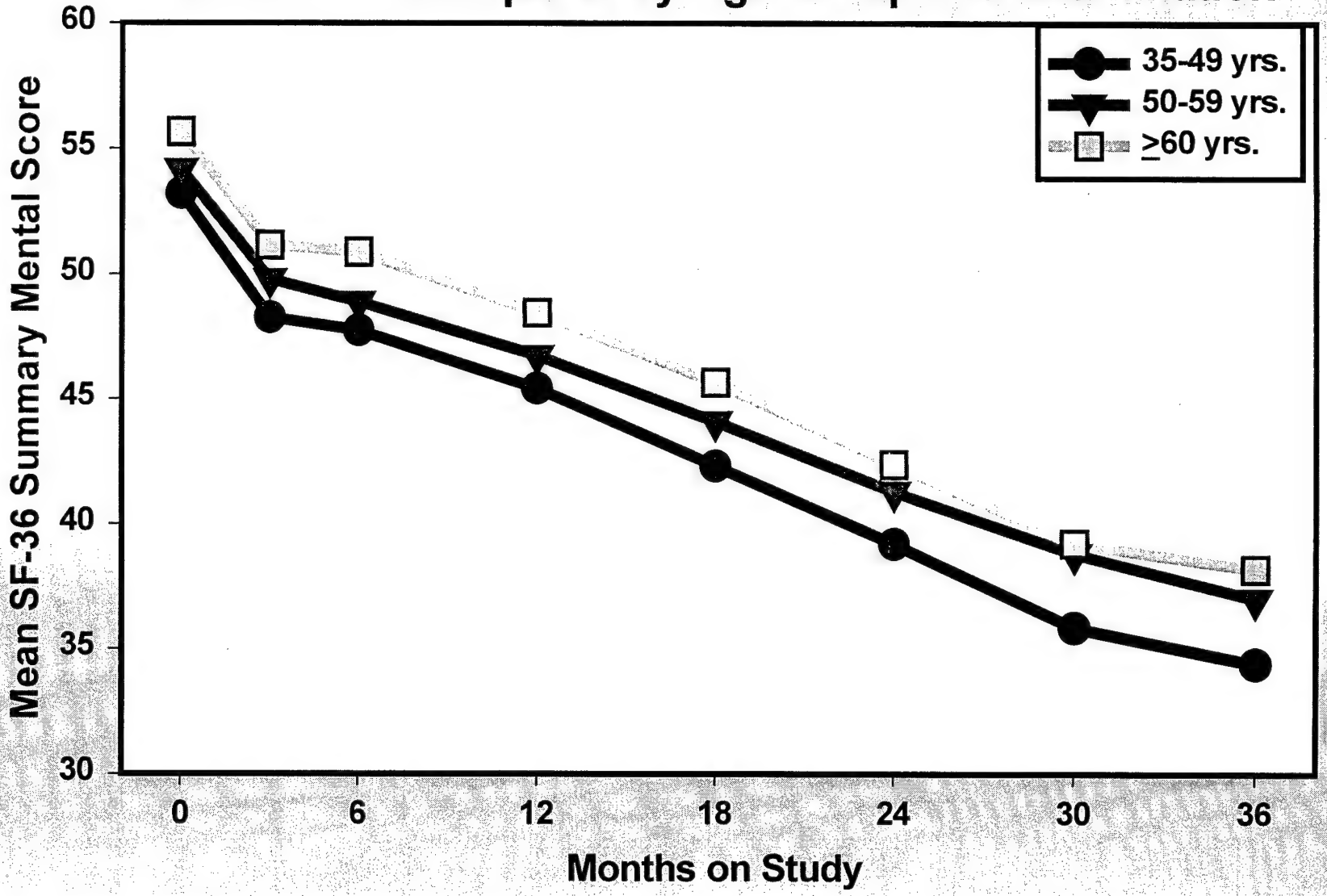

Mean SF-36 Summary Physical Scores
for BCPT Participants by Arm and Examination
Placebo
Tamoxifen
Mean SF-36 Summary Physical Score
60
55
50
45
40
35
30
0
6
12
18
24
30
36
Months on Study

Mean SF-36 Summary Mental Scores for BCPT Participants by Arm and Examination

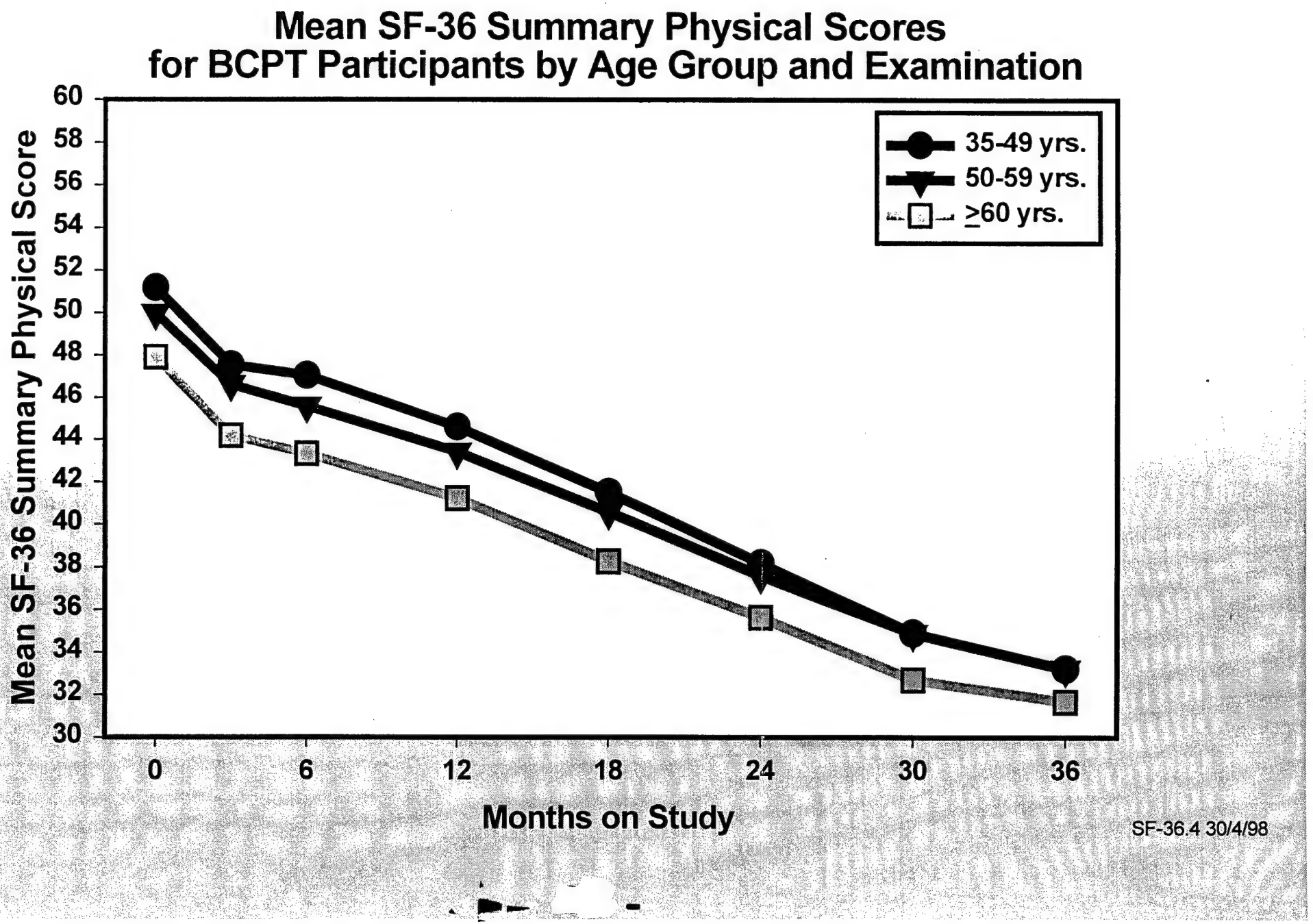


SF-36.2 30/4/98

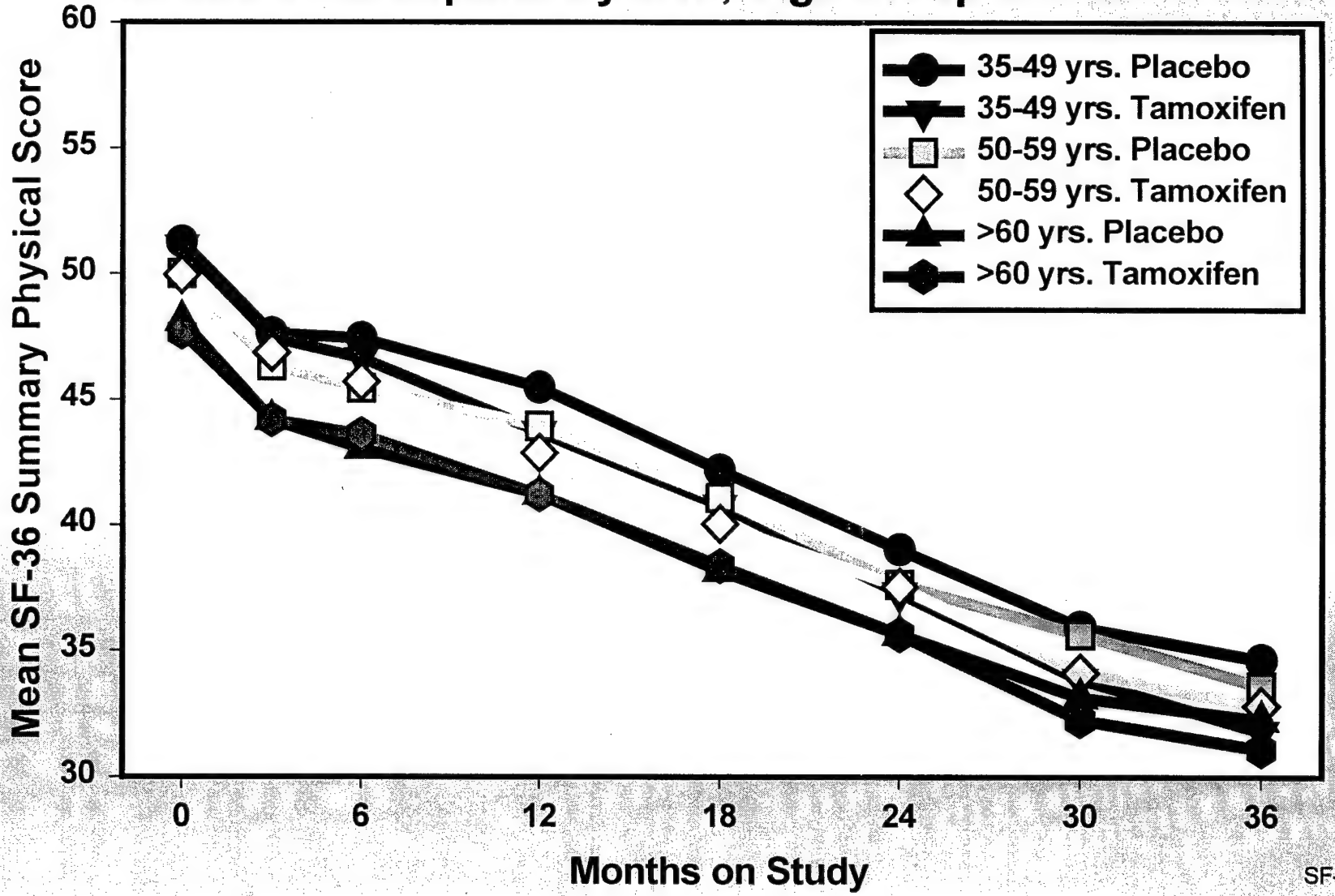
Mean SF-36 Summary Mental Scores for BCPT Participants by Age Group and Examination



SF-36.3 30/4/98

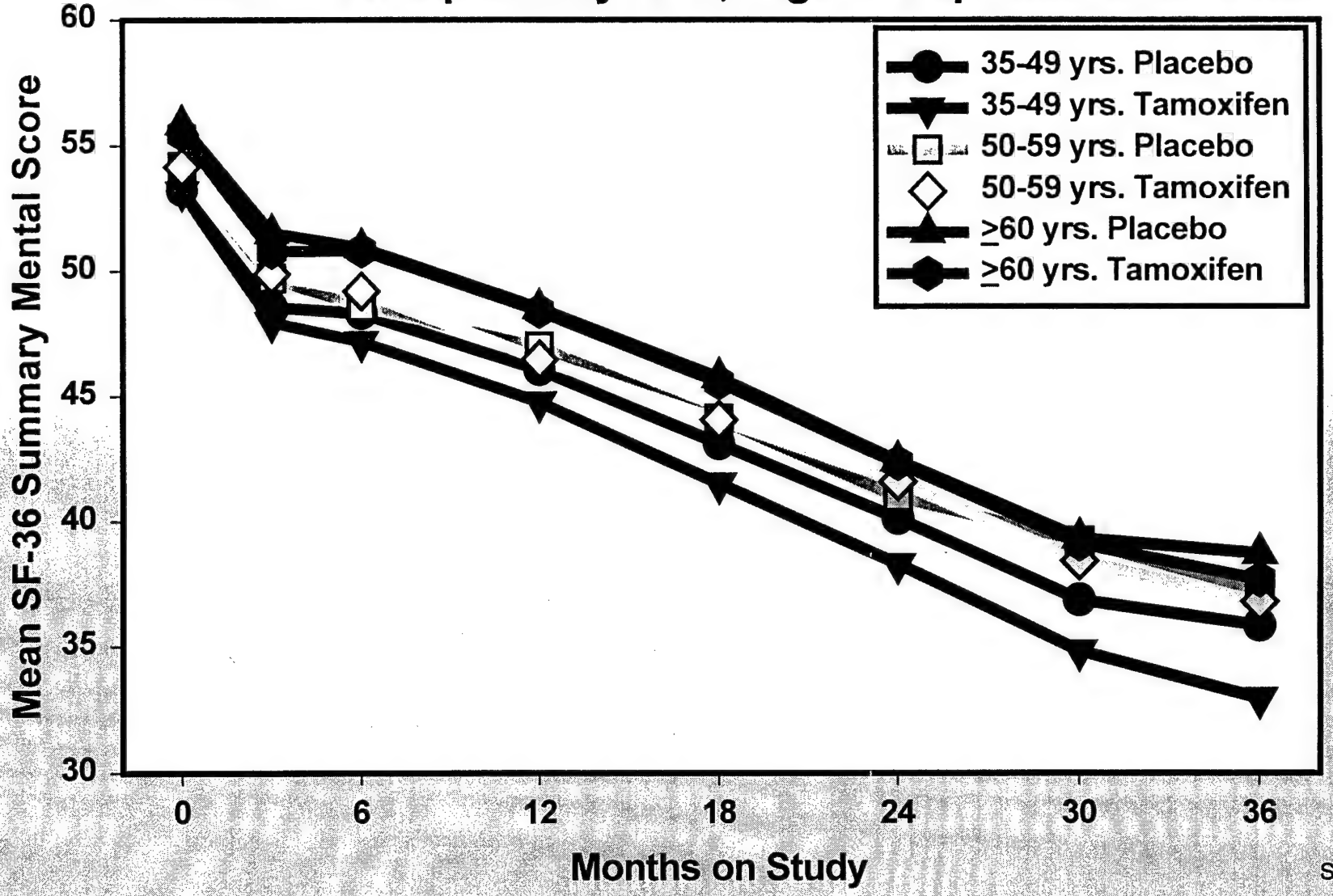

Mean SF-36 Summary Physical Scores
for BCPT Participants by Age Group and Examination
Mean SF-36 Summary Physical Score
60
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
35-49 yrs.
50-59 yrs.
≥60 yrs.
0
6
12
18
24
30
36
Months on Study
SF-36.4 30/4/98

Mean SF-36 Summary Physical Scores for BCPT Participants by Arm, Age Group and Examination



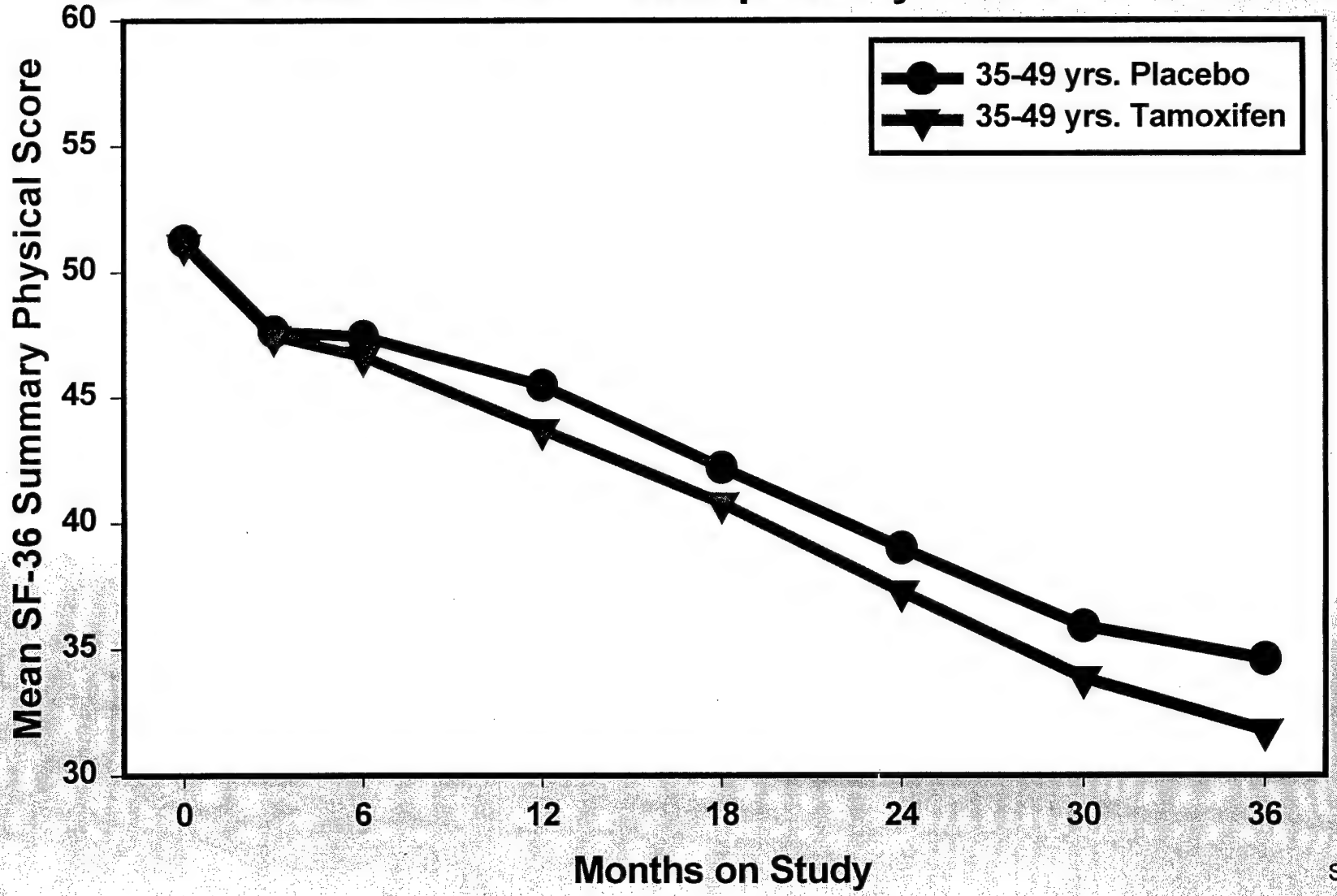
SF-36.5 30/4/98

Mean SF-36 Summary Mental Scores for BCPT Participants by Arm, Age Group and Examination



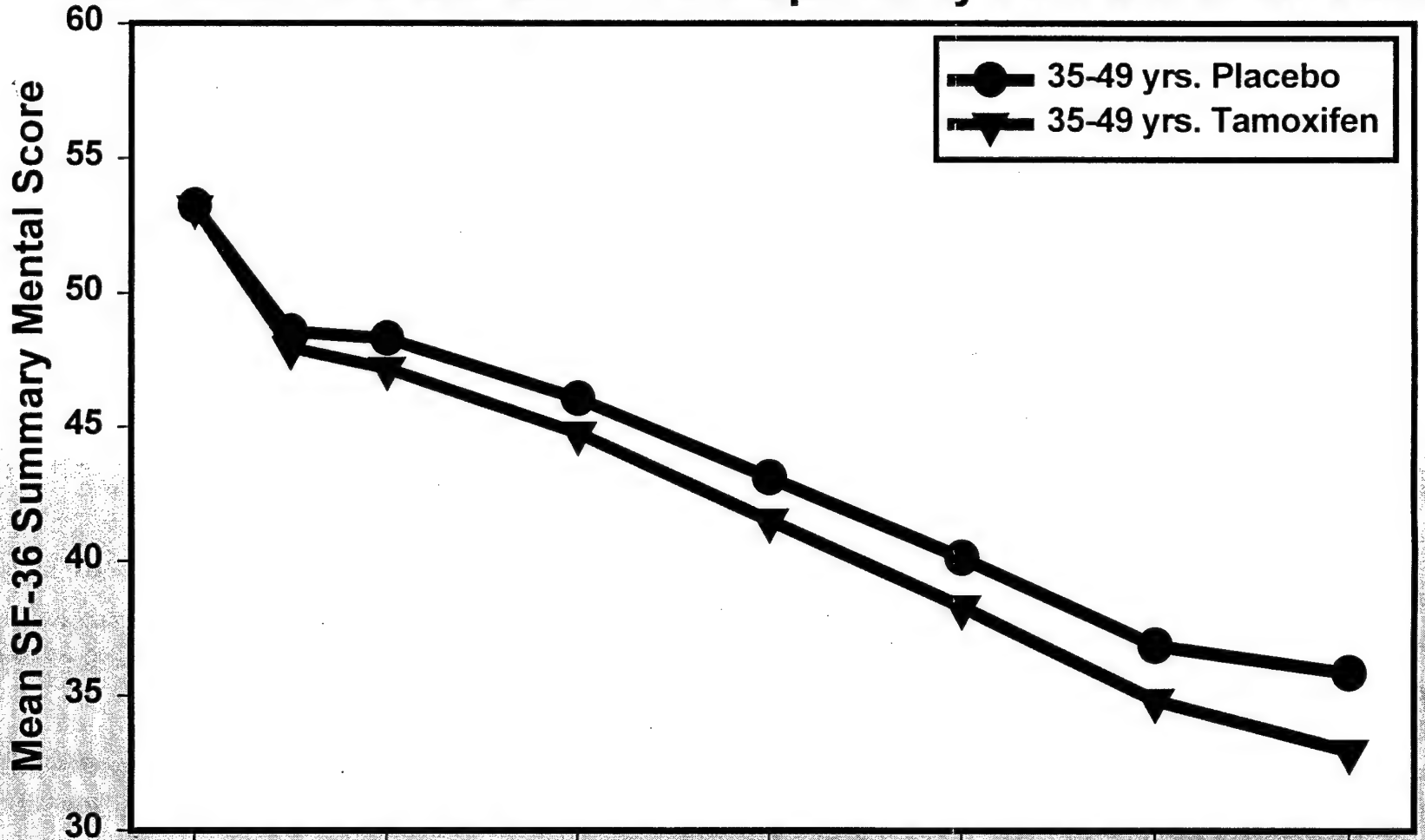
SF-36.6 30/4/98

Mean SF-36 Summary Physical Scores for 35-49 Year-Old BCPT Participants by Arm and Examination



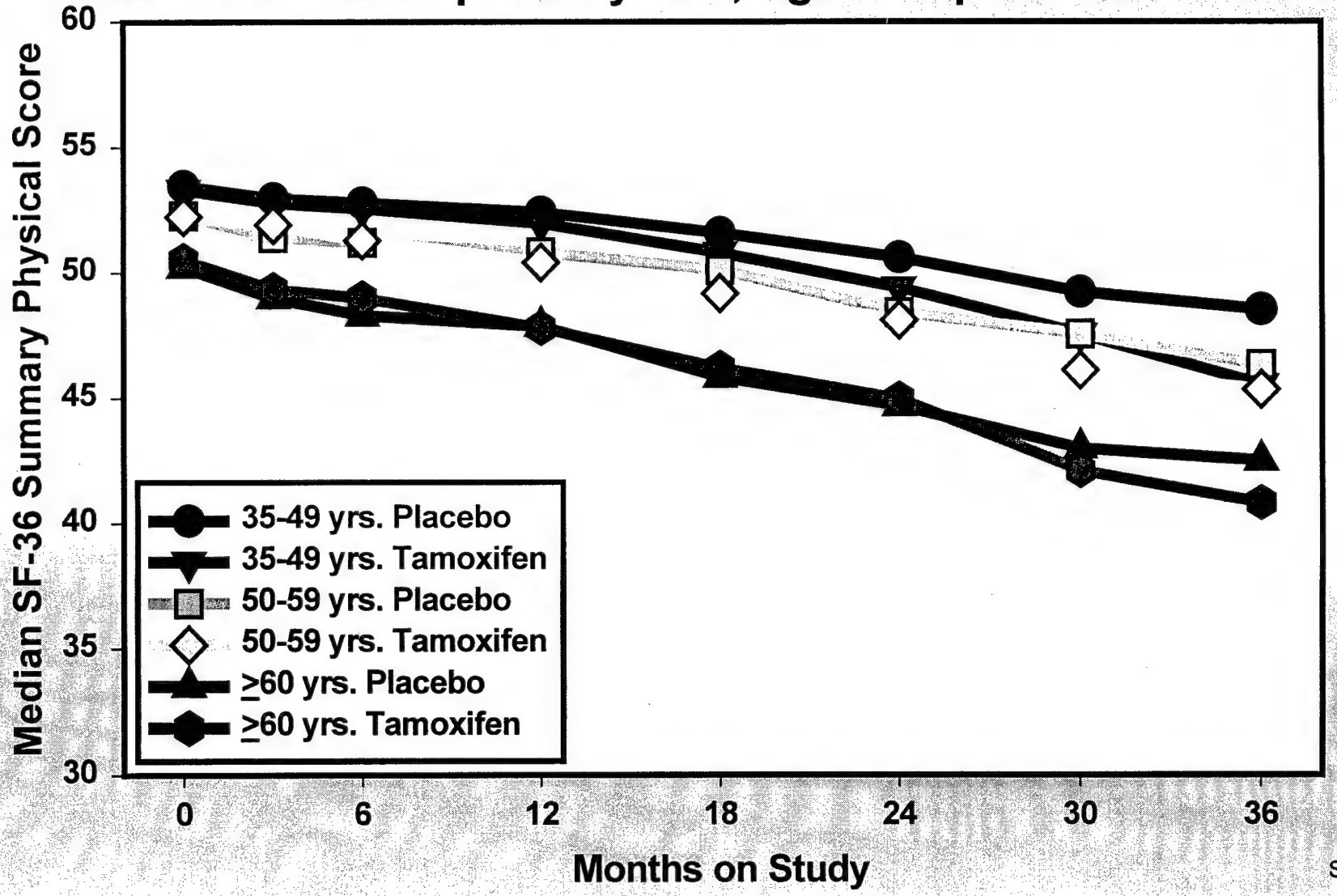
SF-36.7 30/4/98

Mean SF-36 Summary Mental Scores for 35-49 Year-Old BCPT Participants by Arm and Examination



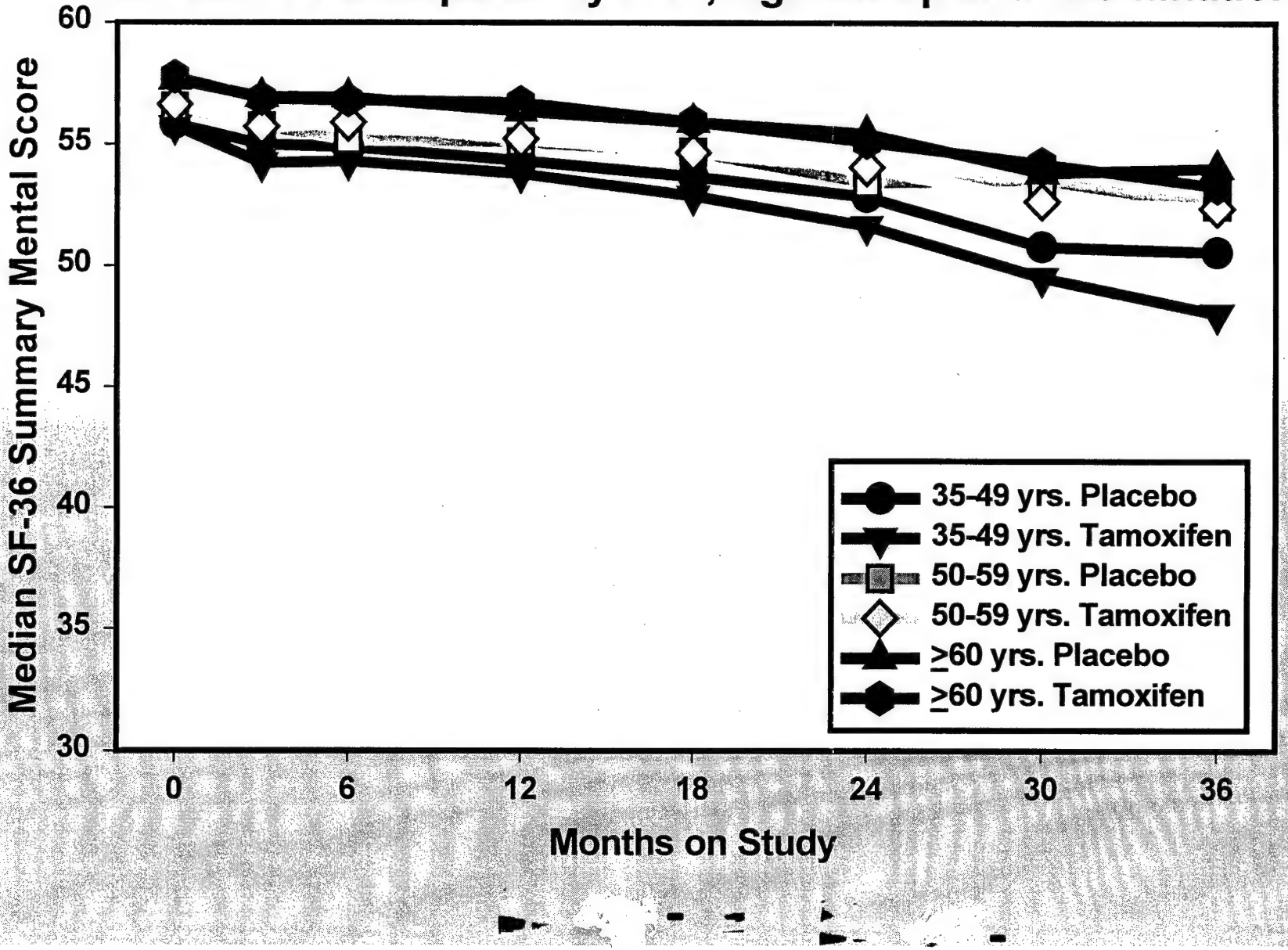
SF-36.8 30/4/98

Median SF-36 Summary Physical Scores for BCPT Participants by Arm, Age Group and Examination

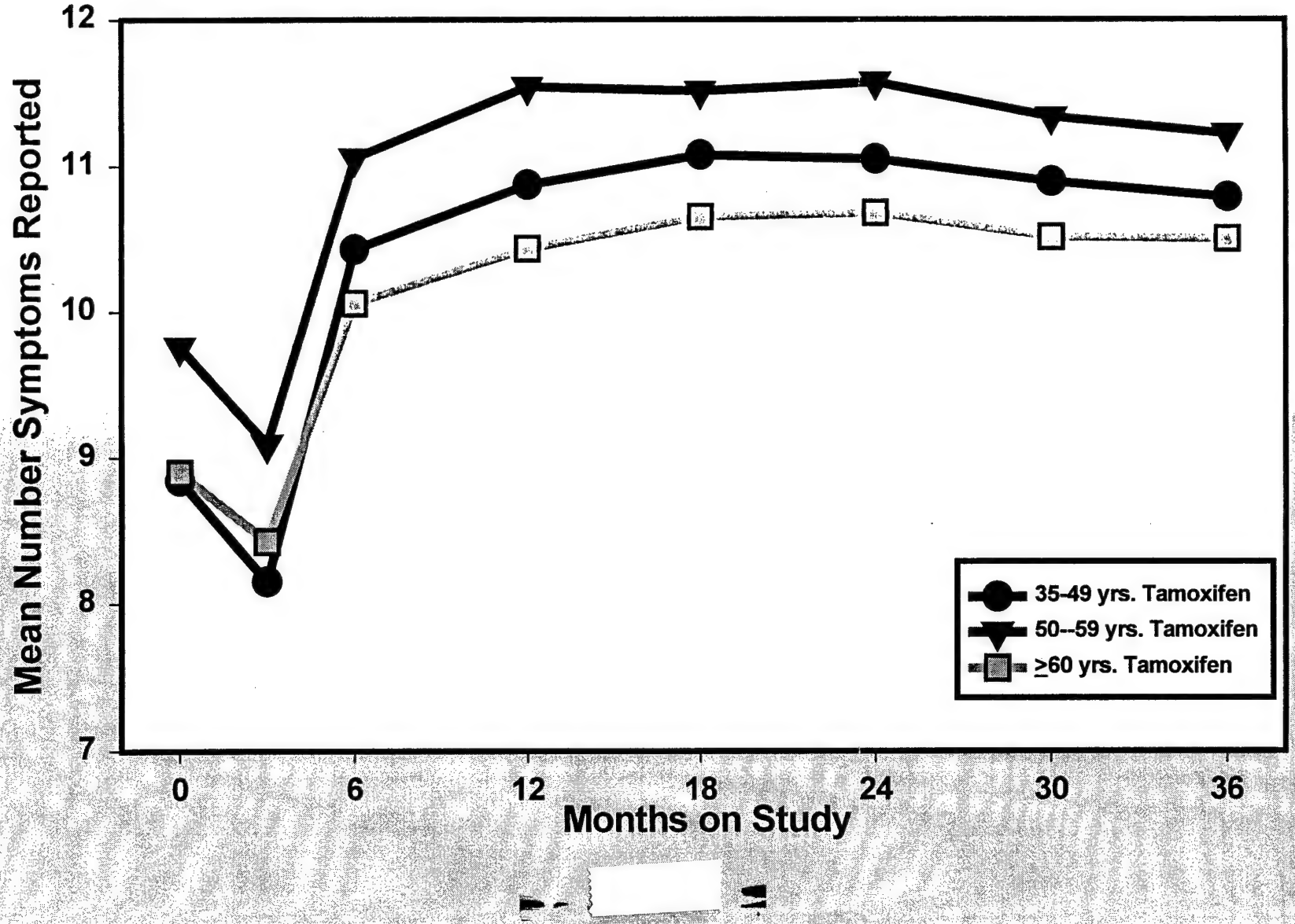


SF-36.9 30/4/98

Median SF-36 Summary Mental Scores for BCPT Participants by Arm, Age Group and Examination

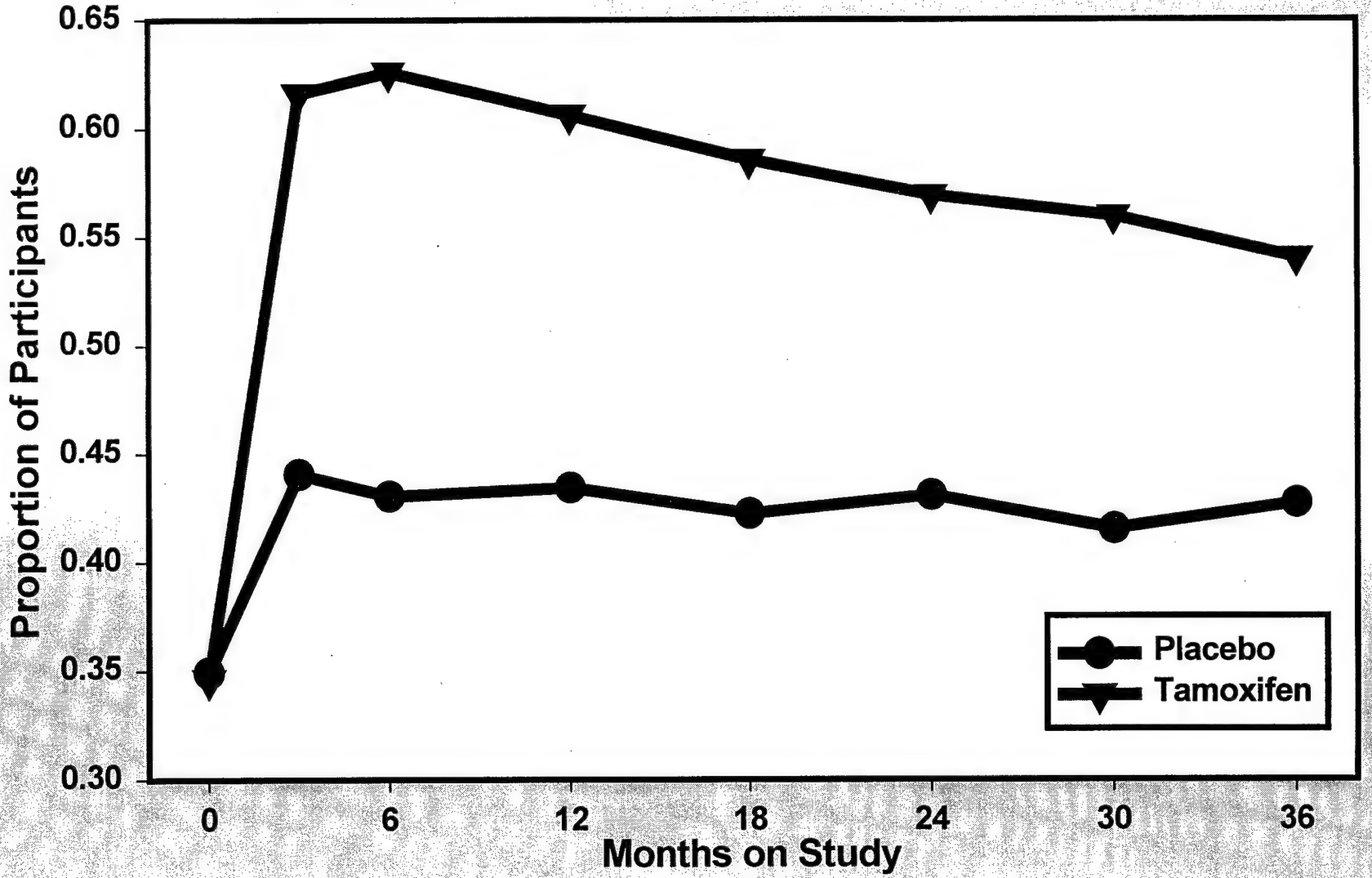


Mean Number of Symptoms reported by BCPT Participants In the Tamoxifen Arm, by Age Group and Examination



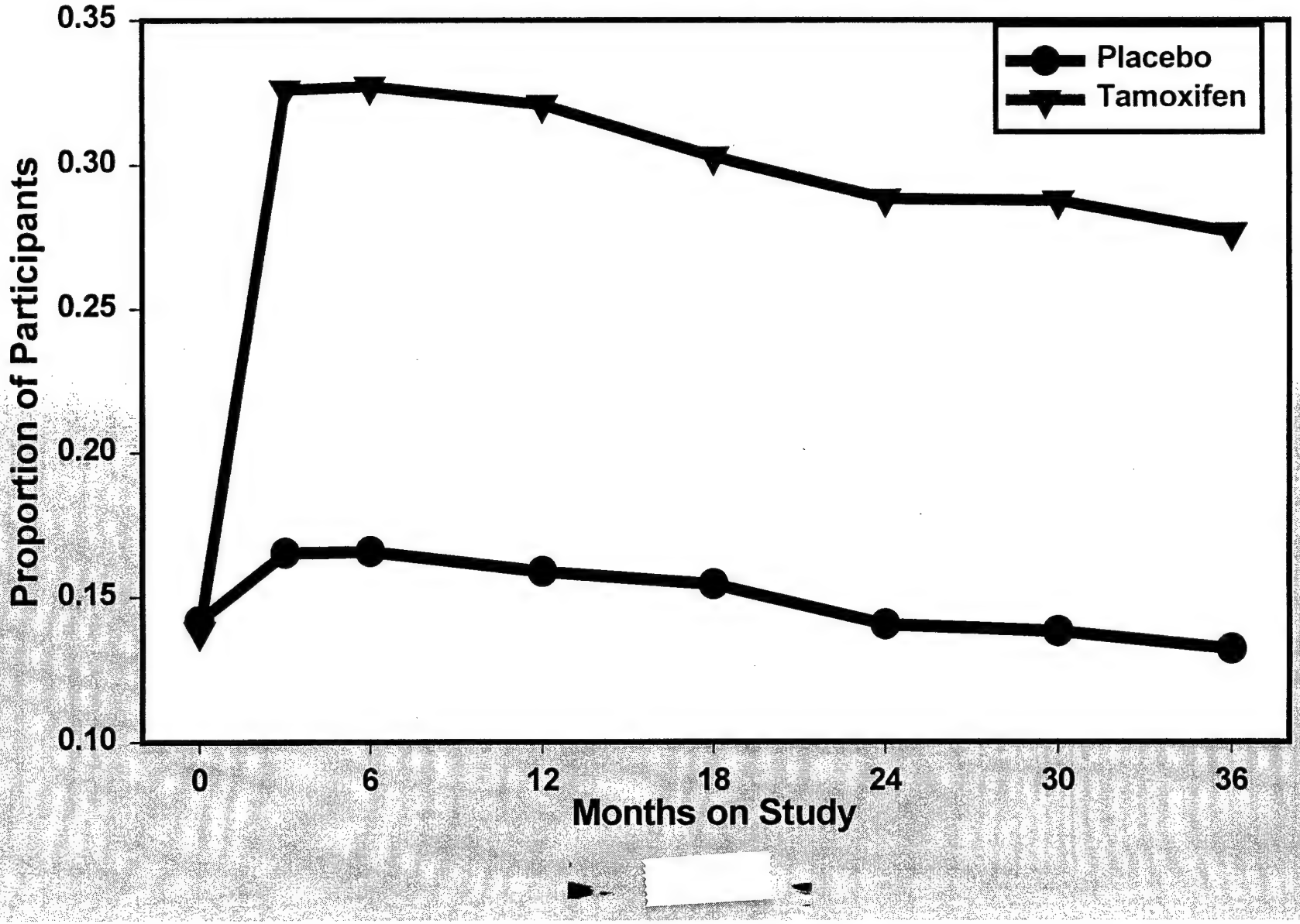
SX4 28/4/98

Proportion of BCPT Participants Reporting Hot Flashes by Arm and Examination



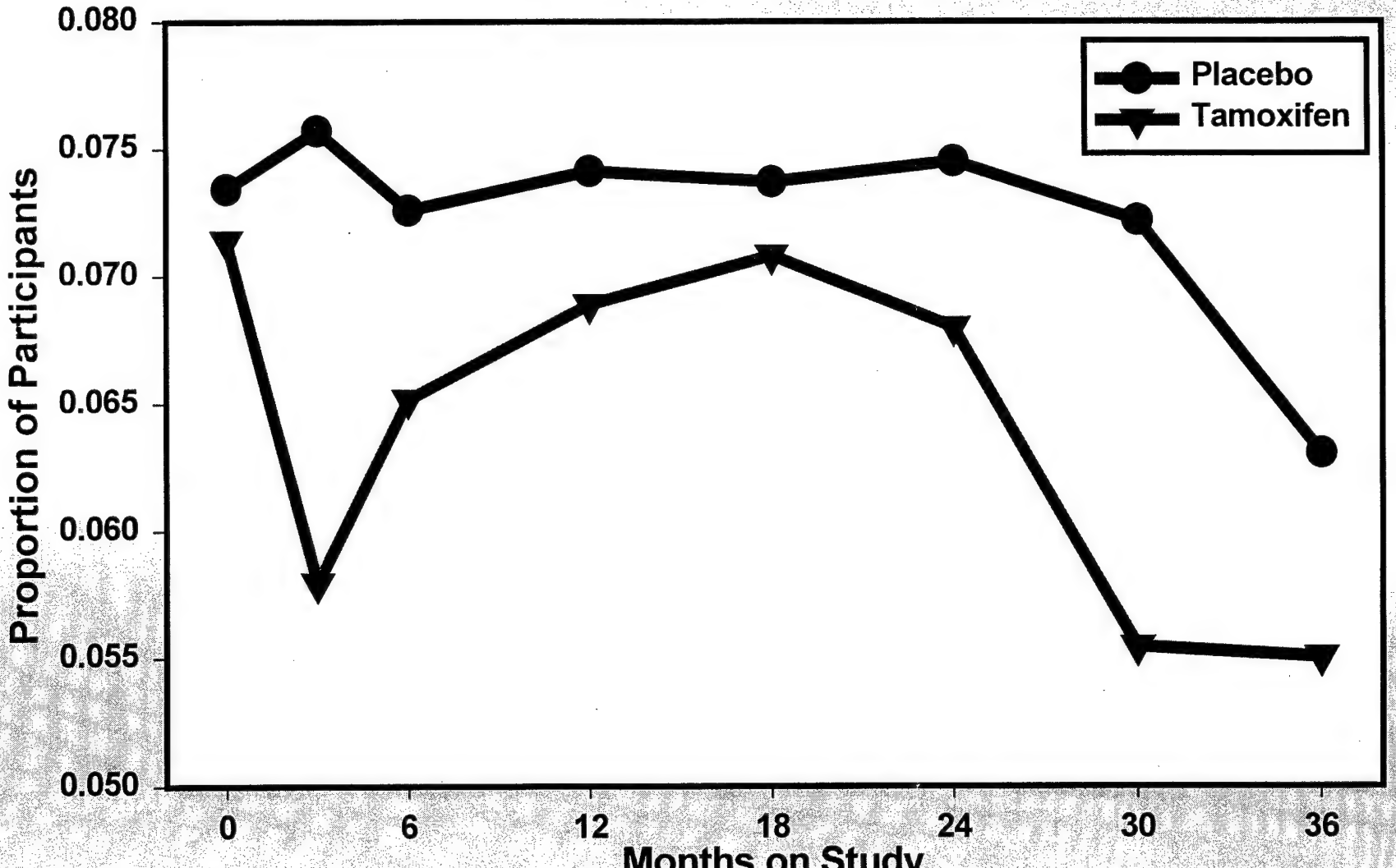
SX5 28/4/98

Proportion of BCPT Participants Reporting Vaginal Discharges by Arm and Examination



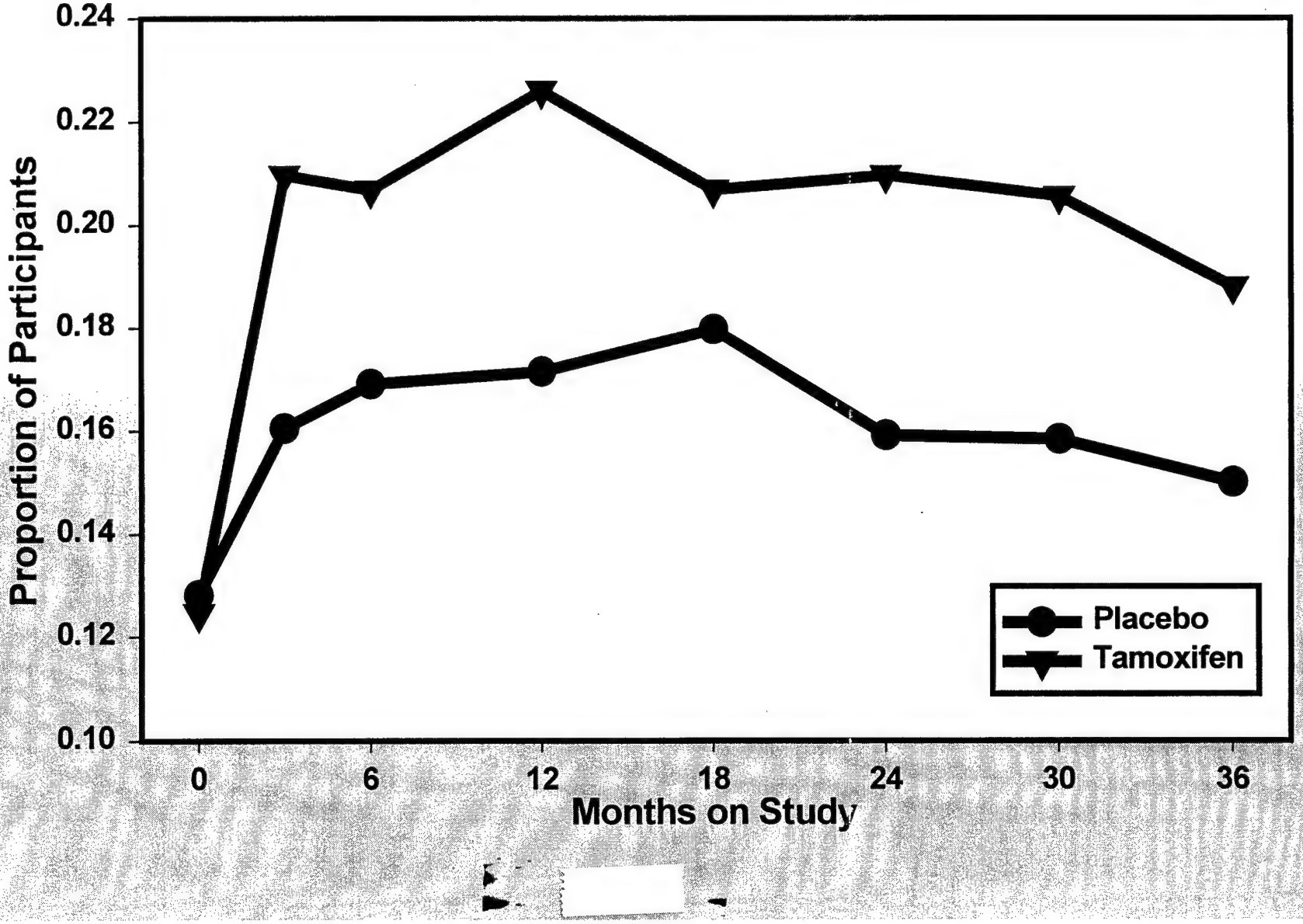
SX6 28/4/98

Proportion of BCPT Participants Reporting Vaginal Bleeding or Spotting by Arm and Examination



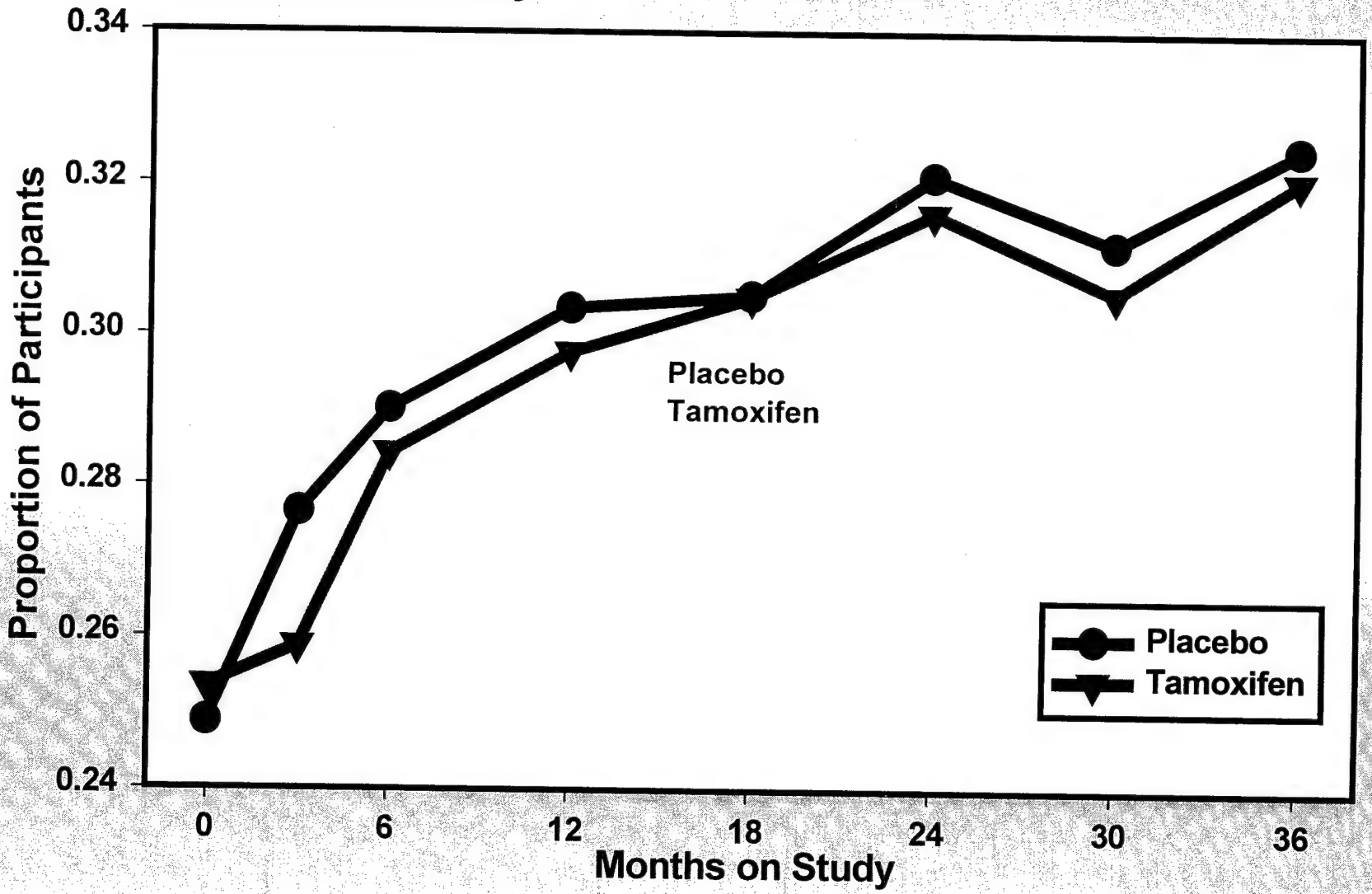
SX7 28/4/98

Proportion of BCPT Participants Reporting Genital Itching or Irritation by Arm and Examination



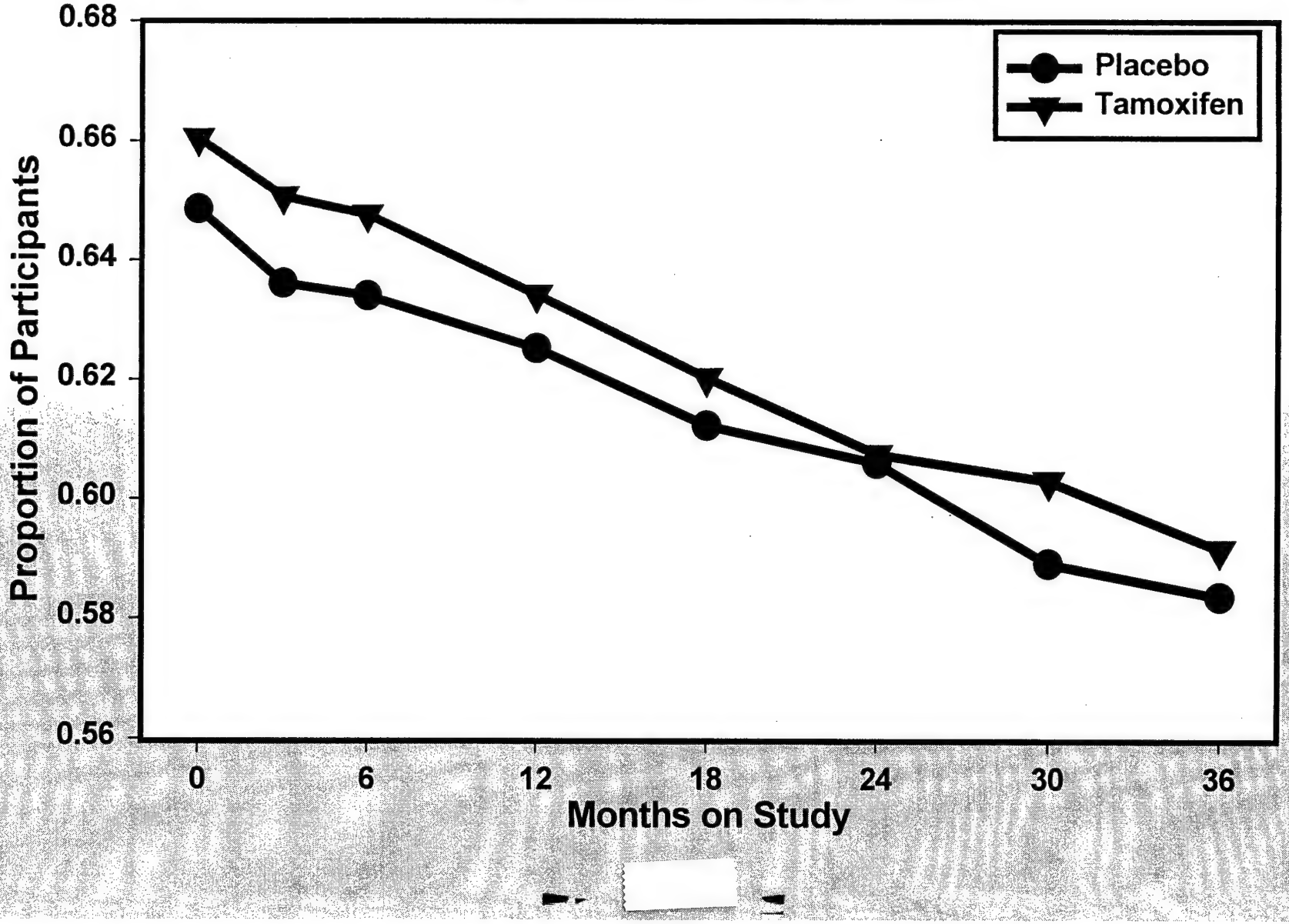
SX8 28/4/98

Proportion of BCPT Participants Reporting Vaginal Dryness by Arm and Examination



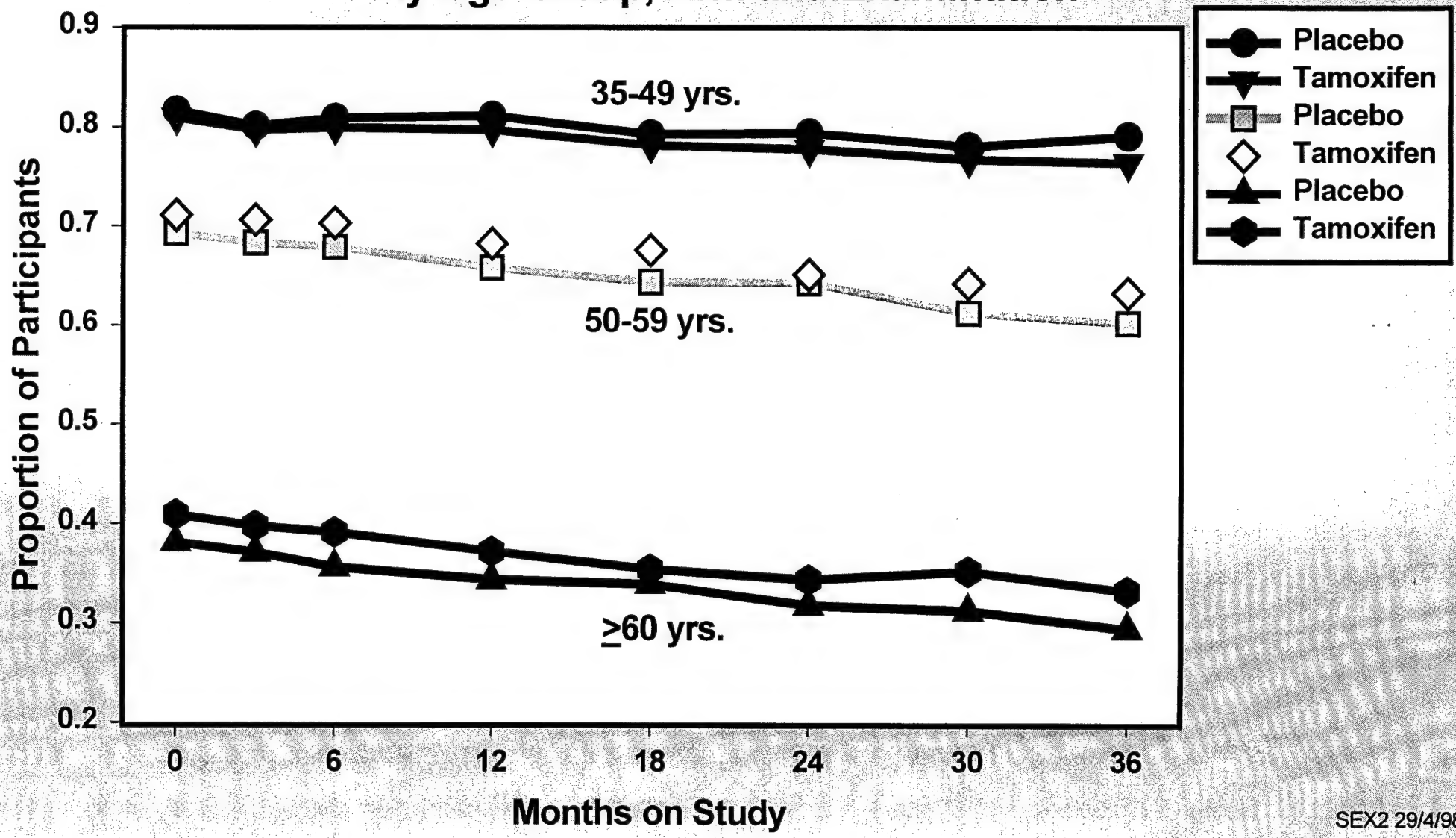
SX9 28/4/98

Proportion of BCPT Participants Sexually Active During Past Six Months by Arm and Examination



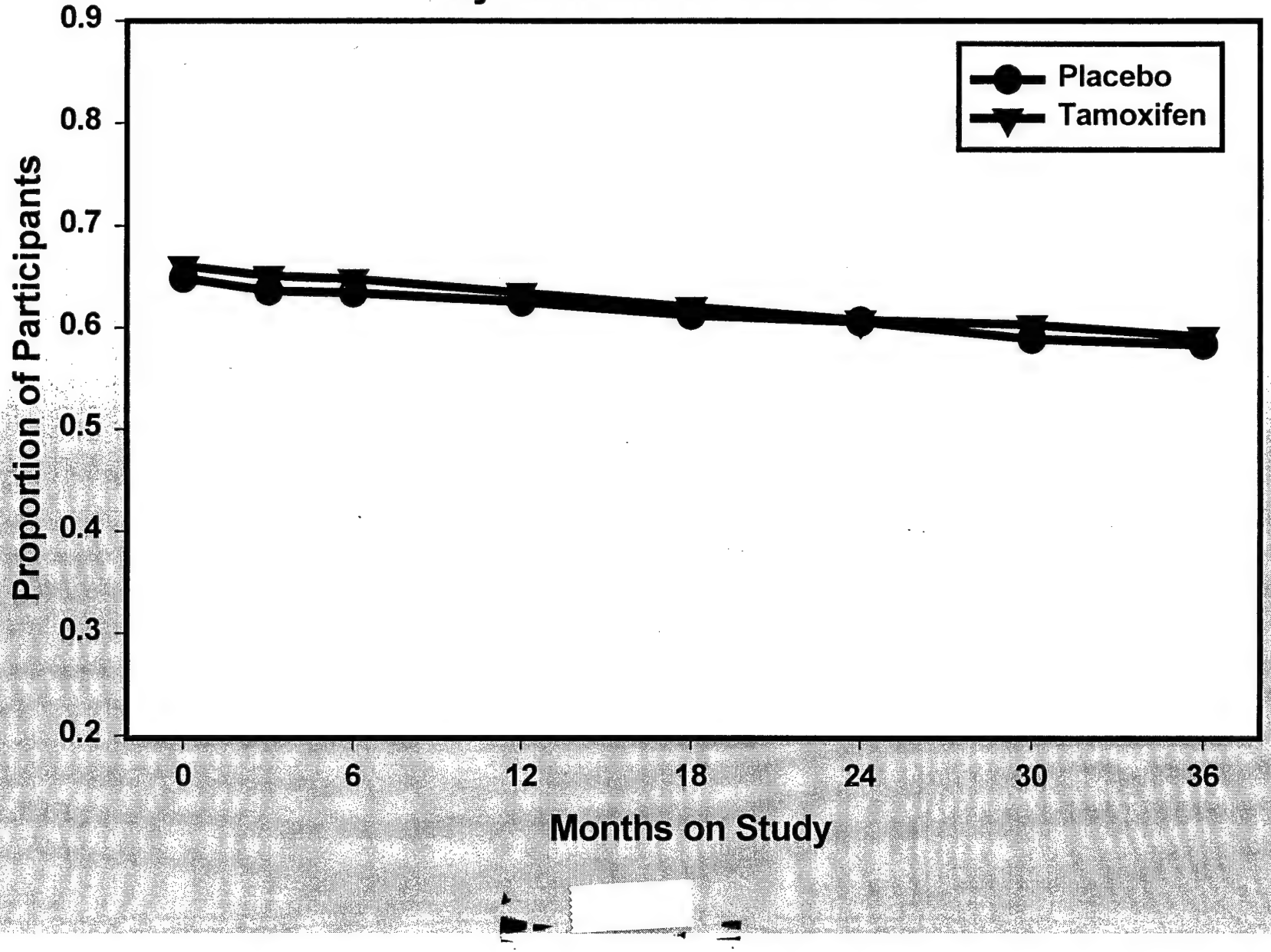
SEX1 29/4/98

Proportion of BCPT Participants Sexually Active During Past Six Months by Age Group, Arm and Examination



SEX2 29/4/98

Proportion of BCPT Participants Sexually Active During Past Six Months by Arm and Examination



SEX3 29/4/98

Electronic Monitoring of Participant Adherence in the NSABP Breast Cancer Prevent Trial (BCPT)

Richard Day, Ph.D.
David F. Cella, Ph.D.
Patricia Ganz, M.D.
Joseph P. Costantino, Ph.D.

National Surgical Adjuvant Breast and Bowel Project (NSABP)
University of Pittsburgh, Pittsburgh, PA

The NSABP BCPT

- Primary Objective: To test the efficacy of TAM in preventing invasive breast cancer and coronary heart disease
- Carried out in 119 nucleus centers in the US and Canada
- Cohort of 13,388 high risk women, 35-80 years-old
- Women were randomized to a placebo or 20 mg of TAM daily for 5 years.
- Scheduled follow-up examinations were at 3, 6 and 12 months and every 6 months thereafter for 7 years

Treatment Schedule and Delivery

- Participants were instructed to take two 10 mg tablets daily
- Tablets were provided in bottles containing a 3 month supply of 200 tablets
- Participants were given one bottle of tablets at baseline and the 3 month follow-up examination, then two bottles at each succeeding 6 month follow-up

BCPT Criterion for "Adequate Participant Adherence"

≥75% of tablets taken on a daily schedule,

that is,

complete treatment adherence on every 3 out of 4 days

BCPT Adherence Monitoring

routine techniques:

Pill Counts

Participant Self-Report (preceding 4 weeks)

experimental technique:

Microelectronic Monitoring System (MEMS)

Collaborating PI's and Clinical Centers in the MEMS Adherence Study

Contacted Apprx – got access to sufficient caps for 100 – subjs. – centrally read.

Dr. David Cella, Rush Presbyterian Hospital, Chicago IL

Dr. Patricia Ganz, UCLA Medical Center, Los Angeles CA

Dr. Mary Daly, Fox Chase Cancer Center, Philadelpha PA

Dr. Julia Rowland, Georgetown University, Washington DC

Dr. Janet Wolter, Rush Presbyterian Hospital, Chicago IL

Objectives of the MEMS Adherence Study

primary :

- **Assess the feasibility and benefits of using an electronic device to monitor treatment adherence in the BCPT**

adherence w/ MEMS caps.

secondary:

- **Estimate short-term adherence rates for a series of BCPT participants**

- **Compare estimated adherence rates derived from the MEMS to rates obtained from pill counts and participant self-reports**

Participant Recruitment to the MEMS Adherence Study

center:	*n:*
Fox Chase	25
Georgetown	22
Rush-Presbyterian	24
UCLA	26
TOTAL	97

S8 9/5/98

Characteristics of BCPT Participants in the MEMS Adherence Study

age:	*n:*
35-49 yrs.	43 (44%)
50-59 yrs.	39 (40%)
60+ yrs	15 (16%)

relative risk:	*n:*
≤ 3.00	14 (15%)
3.01-5.00	39 (40%)
≥ 5.01	44 (45%)

Microelectronic Monitoring of BCPT Participants (1)

cumulative monitoring days mos 1-6:

mos. 1-3	7,962 days
mos. 4-6	6,544 days
Total	14,506 days

cumulative cap openings mos. 1-6:

0 cap openings	7%
1 cap opening	91%
2 cap openings	2%
3+ cap openings	<1%

S10 9/5/98

Microelectronic Monitoring of BCPT Participants (2)

days monitored mos. 1-6:

Mean	**148.6 days**
SE	**5.4 days**
Median days	**179.0 days**

missing data points mos. 1-6:

cap failures*	**6 (33%)**
participant refusals	**3 (17%)**
other	**9 (50%)**

****cap failure rate = 3.1%***

S11 9/5/98

Proportions of Participants Estimated to Show Sufficient Adherence by Various Monitoring Techniques

technique:	*time period: mos. 1-3*	*mos. 4-6*	*overall*
Pill count	**95%**	**94%**	**90%**
Self-report	**96%**	**90%**	**87%**
MEMS	**95%**	**90%**	**88%**

S12 9/5/98

Absolute Proportion of Agreement Between BCPT Adherence Monitoring Techniques Regarding Sufficient vs Insufficient Adherence

	mos. 1-3		*mos. 4-6*	
	MEMS	**pill count**	**MEMS**	**pill count**
pill count	**.957**	**n/a**	**.975**	**n/a**
self-report	**.967**	**.989**	**.963**	**.959**

S13 10/5/98

Unweighted Kappas for Agreement Between BCPT Adherence Monitoring Techniques Regarding Sufficient vs Insufficient Adherence

	mos. 1-3		*mos. 4-6*	
	MEMS	**pill count**	**MEMS**	**pill count**
pill count	**.557***	**n/a**	**.820***	**n/a**
self-report	**.650***	**.883***	**.781***	**.729***

***P<0.001 (H_0: κ=0)**

S14 10/5/98

Estimated Cost* of Using the MEMS in the BCPT

	per year	*total cost*
1,000 particpants in 10 centers	**$160 K**	**$800 K**
all BCPT parts.	**$2.1 million**	**$10.5 million**

*based on APREX Corp. quotes; covers caps, cap readers and software

Aspects of Research Design and Treatment Agents Affecting the Decision to Use MEMS

- **The pharmacokenetic characteristics of the treatment agent being tested** – flexible dose routine – should preventive trials be carried out w/ other types of drugs?
- **The physical characteristics of the treatment agent and the pill distribution system**
- **The underlying objectives (or philosophy) of the proposed clinical trial**

Conclusions from the BCPT MEMS Adherence Study

From a cost/benefit perspective, electronic monitoring systems are not an optimal technique for adherence monitoring in large-scale chemoprevention trials like the BCPT.

Electronic monitoring systems are best suited to more intensive, small-scale trials that are focused primarily on biological efficacy and can implement active forms of adherence monitoring and adherence support.

APPENDIX

d. P-1 Initial HRQL Communication:
Day R, Ganz PA, Costantino JP, HRQL and Breast Cancer Prevention:
A Report from the P-1 Study.

Second Draft 9/20/98

Health-Related Quality of Life and Tamoxifen in Breast Cancer Prevention: A Report of the NSABP P-1 Study

Richard Day, Ph.D., Patricia A. Ganz, M.D., Joseph P. Costantino, Dr. P.H.

Key Words: quality of life, tamoxifen, breast cancer prevention

From the National Surgical Adjuvant Breast and Bowel Project (NSABP) Operational and Statistical Centers. Communications should be addressed to Richard Day, Ph.D., at the Department of Biostatistics, Graduate school of Public Health, 130 DeSoto Street, University of Pittsburgh, Pittsburgh, PA 15261. E-mail: rdfac@vms.cis.pitt.edu.

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Abstract

Background: This is the initial report of the findings from the health-related quality of life (HRQL) component of the National Surgical Adjuvant Breast Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT; P-1), a large multi-center prevention trial with the primary aim of evaluating whether 5 years of tamoxifen therapy reduces the incidence of invasive breast cancer in women at an increased risk for the disease.

Purpose: To provide a concise overview of the P-1 study HRQL findings, together with an assessment of their clinical and functional implications for the use of tamoxifen in a preventative context.

Methods: This report covers the baseline HRQL examination and the first 36 months of follow-up data on 11,064 women recruited over the first 24 months of the study. Summary findings are presented from the HRQL Questionnaire which was composed of the Center for Epidemiological Studies – Depression Scale (CES-D), the Medical Outcomes Study (MOS) Short Form (SF-36), the MOS sexual functioning scale, and a symptom checklist (SCL).

Results: Participants in the P-1 study were predominately white; well-educated, professional and technical women, reporting a middle to upper middle class family income. No differences were found between the trial arms for the proportion of participants scoring above the clinical cut-off on the CESD. No consistent or functionally significant differences were found between the two trial arms with regard to the summary physical and mental component scores on the SF-36. The mean number of symptoms reported on the SCL was consistently different by trial arm (TAM>placebo) and tended to be associated with the types of neurovascular and gynecological

symptoms already reported for tamoxifen. Significant increases were also found in the proportion of women reporting problems in certain specific domains of sexual functioning (sexual interest and enjoyment, orgasm), but these did not appear to affect overall rates of sexual activity.

Conclusions: The increases in neurovascular, gynecological, and sexual functioning symptoms associated with tamoxifen were neither so frequent nor so severe that they prevented the vast majority of women from effectively coping with them as part of their everyday lives. No evidence was found for an association between tamoxifen use and an increase in the proportion of women reporting clinically significant levels of affective distress and/or depression.

Introduction

This is the initial report of the findings from the health-related quality of life (HRQL) component of the National Surgical Adjuvant Breast Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT; P-1). This objective of this report is to provide a concise overview of the P-1 HRQL findings, together with an assessment of their clinical and functional implications for the use of tamoxifen in a preventative context.

The primary objective of the P-1 study was to evaluate whether 5 years of tamoxifen therapy would reduce the incidence of invasive breast cancer in women at an increased risk for the disease. Secondary objectives were to assess the incidence of ischemic heart disease, bone fractures, and other events like depression that might be associated with the use of tamoxifen. Eligible participants were randomized with equal probability to 20 mg daily of tamoxifen or to a placebo for a planned 5 years.

Detailed descriptions of the rationale, planning and design of the of the BCPT and the HRQL component of the P-1 study have been provided in separate reports (1-3).

Methods

Instruments: The 104 item P-1 HRQL Questionnaire (see 3) was composed of the Center for Epidemiological Studies – Depression Scale (CES-D, 20 items), the Medical Outcomes Study (MOS) Short Form (SF-36, 36 items), the MOS sexual functioning scale (5 items), and a symptom checklist (SCL, 43 items). The questionnaire was scheduled to be administered to all participants at baseline, 3 months and at each succeeding 6 month examination for the planned 5-years of treatment and for 1 year after treatment had been completed.

Participant Cohort and HRQL Data: This report covers the baseline HRQL examination and the first 36 months of follow-up data on 11,064 women recruited over the first 24 months (June1, 1992 to 31 May 1994) of the study. This cohort of women represents 82.6% of the total P-1 accrual (N=13,388). Restrictions were imposed on the initial HRQL report for two reasons. First, limiting our attention to this cohort of women allows us to avoid the potential bias created by events beginning March 1994 (4) which resulted in a suspension of accrual to the P-1 study. Second, a focus on the first 36 months of data collection permits improved control over types of missing HRQL data, since all 11,064 participants should have completed the 8 scheduled examinations prior to the early stopping of the trial in the Spring of 1998 (1).

Statistical Analysis

The P-1 HRQL data set is very complex. It is composed of multiple HRQL instruments, each with its own psychometric properties and research history. This complexity is magnified by the fact that data distributions and patterns of missing data may differ across the various instruments included in the HRQL questionnaire. In addition, sample sizes are very large, resulting in the possibility of statistically significant findings for clinically negligible effects. All of these considerations argue for future detailed analyses of the data from each specific instrument. In this initial report, however, our aims of are essentially descriptive in nature and emphasize basic comparisons of the two trial arms. In making these comparisons, we seek to identify consistent differences between the trial arms using simple non-parametric procedures. Positive findings are independently reviewed to assess their clinical and functional significance for the participants' quality of life. The results from various instruments are routinely stratified by 3 age groups – pre- (35-49 yrs.), peri- (50-59 yrs.) and post-menopausal ($\geq$60 yrs.).

Results

Table 1 summarizes the demographic, medical and behavioral characteristics of our participant cohort of 11,064 women by trial arm. These data show that the participants in the P-1 study were predominately white (96%); well-educated (65% $\geq$ some college), married (70%), professional and technical (68.2%) women, who were currently employed (64.9%) and reported a middle to upper middle class family income (median $39-49,999). None of the variables in Table 1 show a striking imbalance between the two trial arms.

Figure 1 charts the overall proportion of women completing the HRQL questionnaire at each examination. It provides a general measure of comparative participant adherence in the two trial arms. Both trial arms show a consistent and marked decline in adherence across the first 36 months of the study averaging 4.2% per examination in the placebo and 4.6% per examination in the tamoxifen arm. The proportion of adherent participants is less in the tamoxifen than in placebo arm at every one of the seven follow-up examinations (sign test, p=0.0078), with a maximum difference of 3.1% occurring at 36 months.

A number of different demographic, clinical and HRQL variables were examined to investigate whether differences could be detected between the women who failed to complete the HRQL questionnaire by 36 months in the tamoxifen and the placebo arm. These variables included mean age (TAM=53.1 yrs. vs. placebo=53.5 yrs.) and mean relative risk (5.42 vs. 5.43), treatment status (10.1% vs. 10.5% off treatment), prior estrogen use (32.5% vs. 33.3%), mean maximum CES-D score (12.52 vs. 12.46), and mean maximum number of reported symptoms on the SCL (14.2 vs. 13.9). These

comparisons suggested that participants failing to complete the HRQL questionnaire in each arm were similar cohorts of women.

Table 2 shows the proportion of P-1 participants, by age group and examination, scoring above the most frequently used clinical cut-off ($\geq$16) on the CES-D (5,6). The youngest age group (35-49 yrs.) in both arms consistently had the highest proportion of members scoring above the clinical cut-off, followed by the 50-59 yrs. age group (Friedman test, p=0.001 TAM and placebo). The relative risks given on Table 2 show that, for all three age groups, there is no consistent excess of participants in the tamoxifen arm when compared to the placebo arm scoring above the clinical cut-off on the CESD. Similar findings with regard to the relationship between the two trial arms emerged from the analysis of the 5-item mental health subscale on the MOS SF-36 (not shown).

The results of the SF-36 are summarized using the physical and mental component scores (PCS, MCS, 7). These two scores represent aggregate measures that combine data from the 8 subscales generally reported on the SF-36. The PCS aggregates data from the Physical Functioning, Role-Physical, Bodily Pain and General Health subscales, while the MCS draws on data from the Vitality, Social Functioning, Role-Emotional, and Mental Health subscales. The PCS and MCS are scored using norm-based methods; both component scores have a mean of 50 and a standard deviation of 10 in the general US population. This means that the PCS and MCS can be meaningfully compared with one another and their scores have a direct interpretation in relation to the distribution of scores in the general US population.

Figure 2 charts the physical and mental component scores for the tamoxifen and placebo arms at each examination and by age group. As expected, mean PCS declines across the age groups. On follow-up examinations, the tamoxifen arm was consistently lower on the PCS only in the 50-59 yrs. age group (one-sided sign test, p=0.065); however, the absolute differences were very small, approximating 1/10 of a standard deviation. With regard to the MCS, all of the age groups score above the mean MCS for the general US population and no consistent differences emerge between the two trial arms.

Table 3 displays the mean number of symptoms reported on the 43-item SCL by age group and examination. The mean number of symptoms reported was consistently highest in the 50-59 yrs. age group followed by the 35-49 yrs. and ≥60 yrs. age groups (Friedman test, p=0.001 TAM and placebo). The participants in the tamoxifen arm also reported a small but consistent excess in the mean number of symptoms (<1) reported at 19 of the 21 age-stratified the follow-up examinations (one-sided sign test, 35-49 yrs. p=0.0078; 50-59 yrs. and ≥60 yrs. p=0.065).

Table 4 provides information on the proportion of women in the tamoxifen and placebo arms reporting symptoms *at least once* over the period covered by the 7 follow-up examinations. It presents, by age group, the 10 symptoms from the SCL with the greatest relative difference between the two trial arms during the period that the participants were on treatment.

Tables 5 and 6 give detailed information on the reported frequency of hot flashes and vaginal discharge in the trial arms *by age group and examination*. The proportion of participants reporting hot flashes was elevated in the tamoxifen arm in every age

group and at every follow-up examination. Among the participants in tamoxifen arm, the 50-59 yrs. age group had the largest proportion of women reporting hot flashes at each examination (median=69.8%, Friedman test, p=0.001), but the youngest age group (35-49 yrs.) showed the greatest relative increase in proportion of women reporting hot flashes (median rr=1.50, Friedman test, p=0.011). Vaginal discharge was the most consistently elevated symptom in the tamoxifen arm. The youngest age (35-49 yrs.) group that had the greatest proportion of participants reporting vaginal discharge at each examination (median=35.5%, Friedman test, p<0.001) and the oldest age group ($\geq$60 yrs.) reported the greatest increase in this symptom relative to the placebo controls (median rr=3.05, Friedman test, p=0.005).

Figure 3 summarizes the information from the 5 items on the sexual functioning scale. Plate A shows that a small proportion (mean=0.78%) of participants in the tamoxifen arm reported being sexually active during the 6 months prior to each follow-up examination (two-sided sign test, p=0.130) . However, Plates B-E show that a small, but consistently larger percentage of participants in the Tamoxifen arm reported a definite or serious problem in three of the four specific domains of sexual functioning (mean difference, two-sided sign test: B=0.74%, p=0.0312; C=0.93%, p=0.0156; D=0.54%, p=0.453; E=1.24%, p=0.0157) during the follow-up period.

Discussion

We observed in our earlier paper (3) that measuring the impact of new treatments on HRQL is particularly important within the context of disease-prevention and health-promotion trials. Decrements in overall quality of life are likely to have a much greater impact on the subjective appraisal of treatment acceptability and the maintenance of long-term treatment adherence among high-risk but otherwise healthy individuals, than among patients suffering from clinically manifest disease. This report covers the initial HRQL findings from a large, multi-center chemoprevention trial which has shown that tamoxifen reduced the risk of invasive breast cancer in high risk women by 45% during the first 5 years of administration. Given the apparent *clinical efficacy* of tamoxifen in a preventative setting, it is important to assess whether the drug's various secondary effects may act to reduce its *practical efficacy* (8-10).

The cohort of women taking part in the P-1 study clearly were not representative of the general population of high risk women. They were predominately white, well-educated, and middle-class, with a strong professional and technical orientation. The initial HRQL findings presented in this report must be assessed within the context of the socioeconomic and cultural characteristics of the P-1 study cohort.

The sub-cohort of women discussed in this report represent 82.6% of the total study cohort. This sub-cohort was chosen in order to exclude potential accrual biases and to control for the amount and types of missing data. Despite this, we still lost 31.5% of our participants by the 36 month follow-up examination. This proportion closely approximates the 10% per year loss to follow-up rate predicted at the beginning of the P-1 trial and is similar in pattern and number to the adherence data recently reported in

a second large, multi-center chemoprevention trial (11). We have shown that there is only a small difference in the proportion of non-adherent participants in the tamoxifen and placebo arms and that the non-adherent women in both trial arms are generally similar on key demographic, clinical and HRQL variables. Given these considerations, it seems unlikely that that a maximum difference of 3% in the HRQL follow-up rates between the two arms was sufficient to create a significant bias in our between arm comparisons.

Much concern has been previously expressed about a potential relationship between tamoxifen use and the onset of depression (12-17). With regard to the primary screening instrument used in this study, it has been pointed out that, "the items in... (the CES-D) are generally related to affective distress but not to any particular psychiatric disorder" (6). For this reason, the numbers presented on Table 2 do not refer to the prevalence of clinically diagnosable depressive disorders, but instead to the prevalence of clinically significant affective distress that may be associated with a number of specific psychiatric disorders. However, if tamoxifen use was associated with the onset of clinically diagnosable depression, we would have expected to see a consistent excess of individuals scoring $\geq$16 on the CES-D in the tamoxifen arm. No such consistent excess was observed. These findings agreed with the data from the mental health scale on the SF-36.

The MOS SF-36 served in this study as a measure of overall health-related quality of life. For this initial report, have presented data from this instrument in terms of two high-level component scores, one summarizing overall physical functioning and the other overall mental functioning. Neither one of these two scales demonstrated any

consistent, clinically significant differences between the tamoxifen and placebo arms in any age group.

The first clear signs of consistent differences between the tamoxifen and placebo arms were observed in the symptom checklist (SCL). The mean number of symptoms reported on the SCL were consistently different by age group (50-59 yrs. > 35-49 yrs. > 60+ yrs.) and by trial arm (TAM>placebo) on 19 out of 21 follow-up comparisons. The absolute differences between the trial arms were relatively small and tended to be associated with the types of neurovascular, gynecological, and sexual functioning symptoms previously reported for tamoxifen (13,18).

The data from the MOS sexual functioning scale indicate that relatively small (<4.0%), but consistent differences exist between the two arms with regard to the proportion of women reporting definite or serious problems in at least three specific domains of sexual functioning – sexual interest, enjoyment of sex, and having orgasm. These problems do not appear to be age group specific. Despite these findings for specific domains of functioning, there is no evidence that these problems result in a reduction in the overall proportion of women who are sexually active.

Based on these data, we would conclude that tamoxifen use is associated with an increase in specific neurovascular, gynecological, and sexual functioning symptoms. However, the frequency and severity these symptoms are such that they do not appear to have a detectable effect for most categories of participants on large-scale, summary measures of HRQL such as the SF-36 PCS and MCS and reported sexual activity. This suggests to us that the increase in symptoms associated with tamoxifen use was neither so frequent nor so severe that the vast majority of women in our trial could not

effectively cope with them as part of their everyday lives. We also found no evidence on the CES-D or the SF-36 mental health scale for an association in any age group between tamoxifen use and an increase in the proportion of women reporting clinically significant levels of affective distress and/or depression.

The current report was a brief overview of the P-1 study HRQL data, focusing on important clinical and functional implications of tamoxifen use for women's overall health-related quality of life. It will be supplemented in the future by a series of additional methodological and clinical reports that will provide in-depth analyses of the data obtained from each one of the several P-1 study HRQL instruments.

Acknowledgement: Carol Moinpour, Ph.D., Sheela Goshal, Wei Chen, Members of the NSABP Prevention Quality of Life Committee .....

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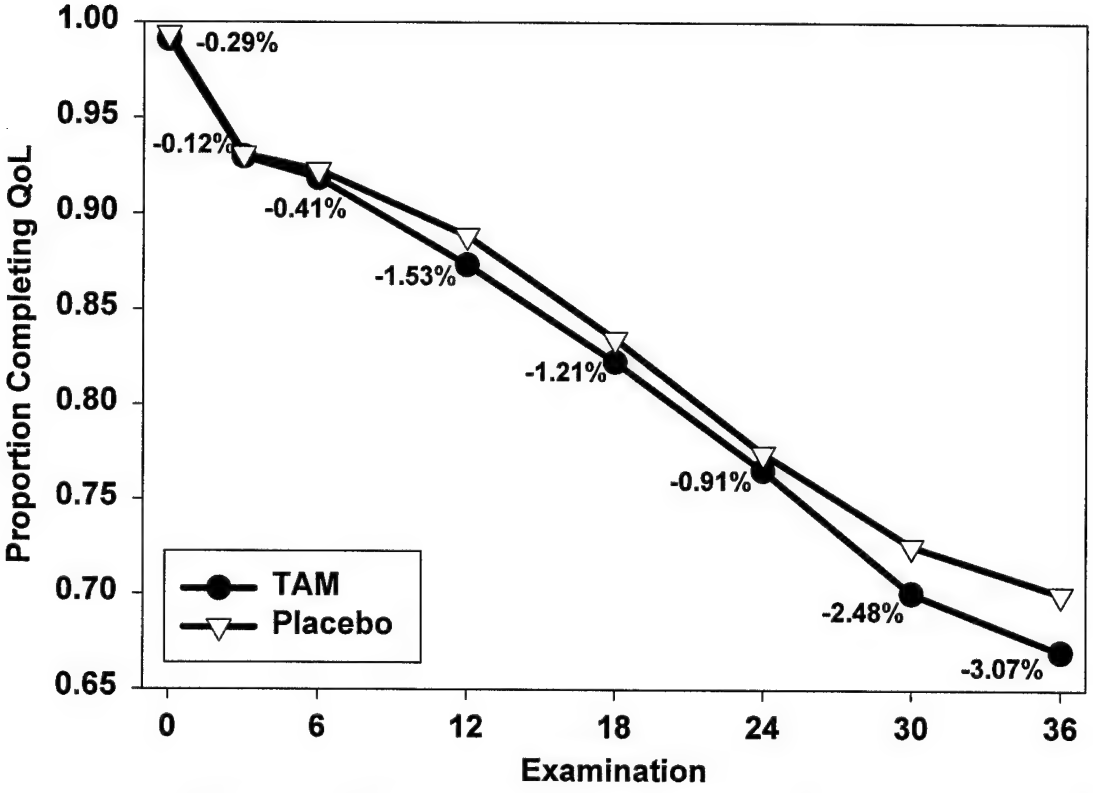
Figure 1
Proportion of Participants in the Tamoxifen and Placebo Arms Completing the QoL Questionnaire by Examination[1]



1. Figures on chart are percent difference between Tam and placebo arms

Figure 2
Mean Scores by Age Group and Examination on Sf-36 Physical and Mental Component Scores

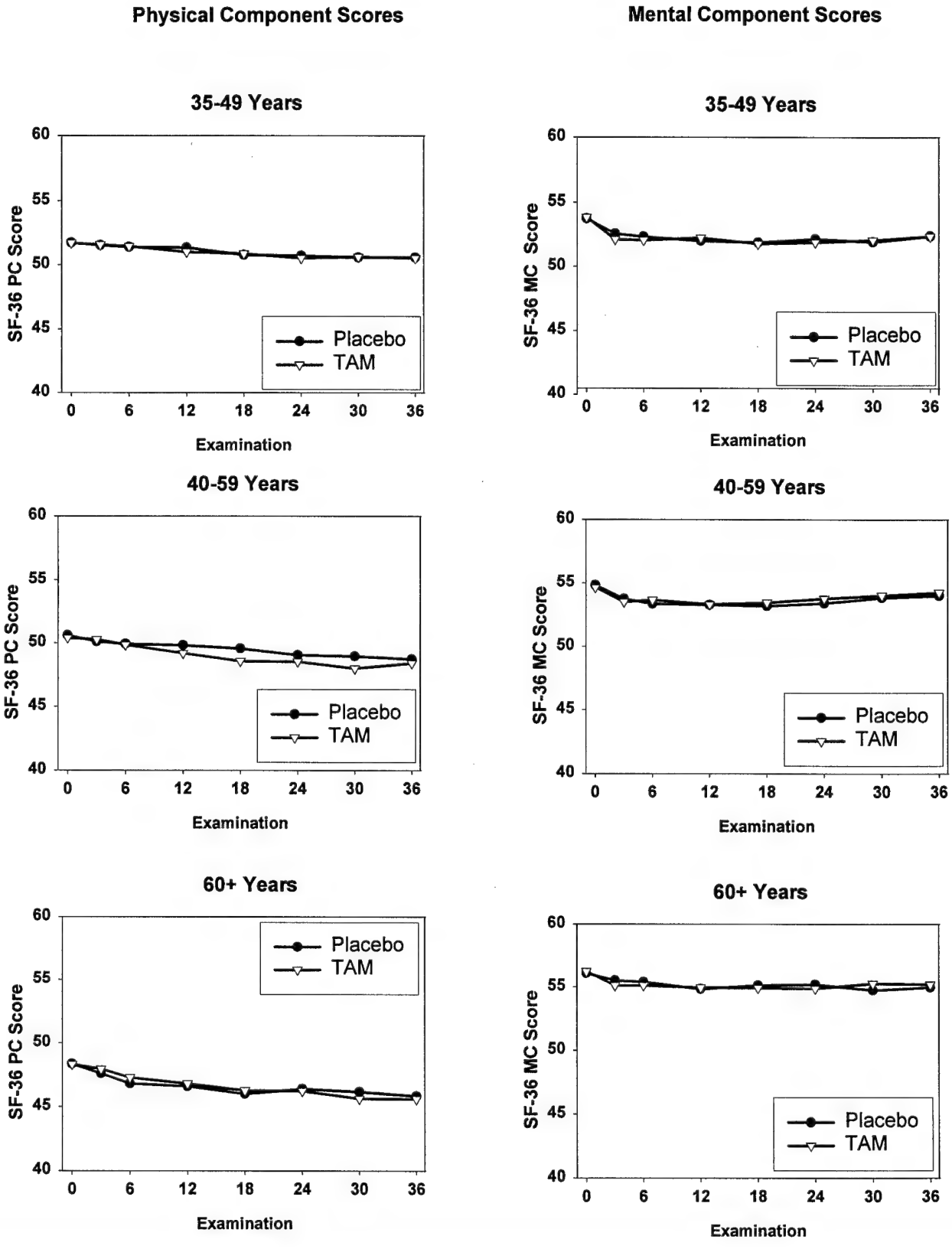


Figure 3
Proportion of Women in the Tamoxifen and Placebo Arms Reporting a Definite or Serious Problem in Past 4 Weeks on MOS Sexual Functioning Scale

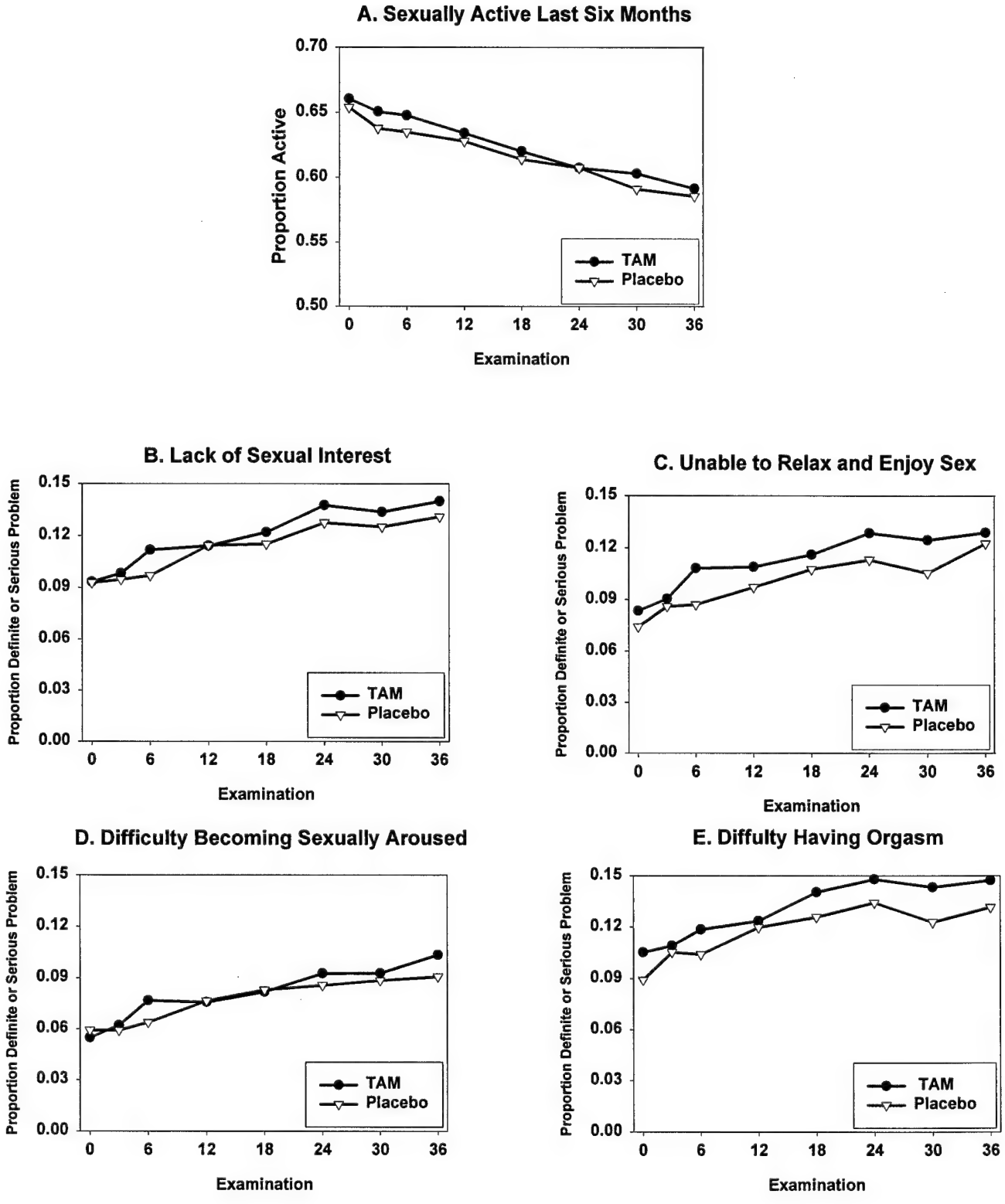


Table 1
Demographic, Clinical and Health Behavior Characteristics of P-1 HRQL Study Participants (N=11,064)

Characteristic	Placebo		Tamoxifen		Total	
	No.	%	No.	%	No.	%
Age						
Mean	53.83 (SD±9.167)		53.82 (SD±9.184)		53.83 (SD±9.175)	
Median	52 (35-79)		52 (35-78)		52 (35-79)	
Ethnicity						
White	5290	95.78	5282	96.00	10572	95.89
Hispanic	63	1.14	49	0.89	112	1.02
Black	88	1.59	95	1.73	183	1.66
Oriental	35	0.63	37	0.67	72	0.65
Native Hawaiian	4	0.07	3	0.05	7	0.06
Native American	13	0.24	11	0.20	24	0.22
Indian Subcontinent	2	0.04	1	0.02	3	0.03
Filipino	9	0.16	6	0.11	15	0.14
Other	19	0.34	18	0.33	37	0.34
Unknown	0	0.00	0	0.00	0	0.00
Education						
Grade school	61	1.11	66	1.20	127	1.16
Some high school	248	4.51	218	3.97	466	4.24
High school graduate	1003	18.23	1009	18.38	2012	18.30
Vocational school	593	10.78	614	11.18	1207	10.98
Some college	1180	21.44	1194	21.74	2374	21.59
Associate degree	349	6.34	349	6.36	698	6.35
College graduate	664	12.07	732	13.33	1396	12.70
Professional school	546	9.92	519	9.45	1065	9.69
Master' s degree	726	13.19	684	12.46	1410	12.83
Doctoral degree	133	2.42	106	1.93	239	2.17
Employment						
Unemployment	239	4.33	229	4.16	468	4.25
Retired	925	16.15	938	17.05	1863	16.90
Full-time homemaker	660	11.95	670	12.08	1330	12.06
Student	30	0.54	33	0.63	63	0.57
Employed full-time	2713	49.12	2682	48.75	5395	48.94
Employed part-time	880	15.93	878	15.96	1758	15.95
On medical leave	25	0.45	24	0.44	49	0.44
Permanently disabled	51	0.92	47	0.85	98	0.89
Occupation						
Homemaker	849	15.37	843	15.32	1692	15.35
Professional	2207	39.96	2188	39.87	4395	39.87
Technical	1573	28.48	1548	28.31	3121	28.31
Services	487	8.82	487	8.85	974	8.84
Operators	92	1.67	94	1.71	186	1.69
Other	315	5.70	341	6.20	656	5.95

Table 1 (contd.)
Demographic, Clinical and Health Behavior Characteristics of P-1 HRQL Study Participants (N=11,064)

Characteristic	Placebo		Tamoxifen		Total	
	No.	%	No.	%	No.	%
Income						
Under $2,000	20	0.37	14	0.26	34	0.32
$2,000 - $4,999	35	0.65	29	0.54	64	0.60
$5,000 - $7,999	73	1.37	59	1.11	132	1.24
$8,000 - $9,000	83	1.55	59	1.11	142	1.33
$10,000 - $12,999	138	2.58	143	2.68	281	2.63
$13,000 - $14,999	97	1.81	109	2.04	206	1.93
$15,000 - $17,999	173	3.24	182	3.41	355	3.32
$18,000 - $19,999	141	2.64	137	2.57	278	2.60
$20,000 - $24,999	411	7.69	398	7.46	809	7.57
$25,000 - $34,999	716	13.39	772	14.47	1488	13.93
$35,000 - $49,999	936	17.51	984	18.44	1920	17.97
$50,000 - $74,999	1153	21.56	1151	21.57	2304	21.56
$75,000 - $99,000	511	9.56	478	8.96	989	9.26
$100,000 or more	564	10.55	521	9.76	1085	10.16
Unanswered	296	5.54	301	5.64	597	5.59
Marital status						
Never married	398	7.21	394	7.16	792	7.18
Presently married	3843	69.58	3876	70.45	7719	70.01
Marriage-like	139	2.52	125	2.27	264	2.39
Divorced	748	13.54	707	12.85	1455	13.20
Widowed	395	7.15	399	7.25	794	7.20
Unknown	0	0	1	0.02	1	0.01
Smoking						
Smoked at least 100 cigarettes in lifetime	2697	48.83	2729	49.60	5470	50.39
Smoked at least 100 cigarettes in lifetime and currently smoke	705	12.76	712	12.94	1417	12.85
Alcohol						
Never use	1138	20.60	1128	20.50	2266	20.55
Some days	4129	74.76	4147	75.37	8276	75.07
Every day	256	4.64	227	4.13	483	4.38
Previous estrogen use	1171	31.98	1838	33.25	3609	32.62
Both ovaries removed	797	14.39	813	14.71	1610	14.55
Menstrual period						
Stopped	3658	66.06	3685	66.67	7343	66.37

Table 2
Proportion of Participants in Tamoxifen Arm with a Clinically Significant Score (≥16) on the CES-D by Age Group and Examination

Examination	Age Group							
	35-49 yrs		50-59 yrs		≥ 60 yrs		Overall	
	TAM	RR[1]	TAM	RR[1]	TAM	RR[1]	TAM	RR[1]
Baseline	.074	1.03	.082	1.28	.058	.918	.071	1.07
3 months	.122	1.10	.104	1.05	.085	1.08	.105	1.08
6 months	.138	1.06	.114	1.00	.093	.910	.117	1.00
12 months	.128	.937	.122	.999	.096	.989	.116	.968
18 months	.139	.892	.126	.918	.101	.929	.123	.908
24 months	.143	1.02	.124	.980	.095	.924	.122	.980
30 months	.142	.978	.107	.961	.104	.934	.120	.959
36 months	.135	.898	.111	1.04	.097	.887	.116	.930

1. relative risk (RR)= TAM/placebo

Table 3
Mean Number of Total Symptoms Reported on Symptom Checklist by Age Group and Examination

Examination	Age Group							
	35-49 yrs		50-59 yrs		≥ 60 yrs		Overall	
	TAM	Diff.[1]	TAM	Diff.[1]	TAM	Diff.[1]	TAM	Diff.[1]
Baseline	8.84	+.114	9.76	+.236	8.89	-.030	9.14	+.110
3 months	9.96	+.319	10.54	-.006	9.63	-.166	10.04	+.077
6 months	10.43	+.564	11.06	+.304	10.06	+.011	10.51	+.322
12 months	10.87	+.521	11.54	+.655	10.43	+.076	10.95	+.429
18 months	11.08	+.614	11.51	+.452	10.65	+.292	11.08	+.469
24 months	11.05	+.733	11.58	+.549	10.68	+.476	11.10	+.602
30 months	10.27	+.227	10.67	+.547	10.15	+.134	10.36	+.299
36 months	10.79	+.386	11.22	+.700	10.50	+.190	10.84	+.426

1. Diff.= TAM-Placebo

Table 4
The 10 Symptoms Reported At Least Once Between Months 3 and 36
With The Largest Relative Difference Between Trial Arms

Age group and Symptom	Relative Risk (TAM/Placebo)	Tamoxifen Arm Proportion(%)
35-49 yrs		
1. Cold sweats	1.61	22.90
2. Vaginal discharge	1.45	62.55
3. Pain in intercourse	1.23	31.57
4. Night sweats	1.22	74.16
5. Hot flashes	1.20	81.28
6. Genital itching	1.17	53.28
7. Ringing in ears	1.13	33.32
8. Constipation	1.11	56.77
9. Vaginal dryness	1.10	46.63
10. Dry mouth	1.07	45.34
50-59 yrs		
1. Cold sweats	1.45	27.00
2. Vaginal discharge	1.36	53.47
3. Genital itching	1.33	45.24
4. Night sweats	1.25	75.88
5. Bladder control (laugh)	1.25	56.94
6. Feeling of suffocation	1.22	14.47
7. Bladder control (other)	1.12	56.82
8. Tendency to accident	1.11	19.53
9. Hot flashes	1.10	86.65
10. Pain in intercourse	1.10	33.65

Table 4 (contd.)
The 10 Symptoms Reported At Least Once Between Months 3 and 36
With The Largest Relative Difference Between Trial Arms

Age group and Symptom	Relative Risk (TAM/Placebo)	Tamoxifen Arm Proportion(%)
≥60 yrs		
1. Vaginal bleeding	2.37	10.92
2. Vaginal discharge	2.33	62.55
3. Cramps	1.31	77.55
4. Genital itching	1.29	40.96
5. Hot flashes	1.24	63.59
6. Night sweats	1.18	47.69
7. Cold sweats	1.15	13.65
8. Decreased appetite	1.14	28.09
9. Bladder control (laugh)	1.14	56.49
10. Constipation	1.13	57.46
Overall		
1. Vaginal discharge	1.61	54.77
2. Cold sweats	1.45	21.40
3. Genital itching	1.23	47.13
4. Night sweats	1.22	66.80
5. Hot flashes	1.20	77.66
6. Pain in intercourse	1.17	28.19
7. Bladder control (laugh)	1.13	52.51
8. Bladder control (other)	1.11	52.83
9. Constipation	1.10	63.59
10. Weight loss	1.07	44.94

Table 5
Proportion of Women Reporting Hot Flashes in Tamoxifen Arm and Relative Risk Compared to Placebo Arm by Age Group and Examination

Examination	Age Group							
	35-49 yrs		50-59 yrs		≥ 60 yrs		Overall	
	TAM	RR[1]	TAM	RR[1]	TAM	RR[1]	TAM	RR[1]
Baseline	.258	0.959	.533	0.989	.268	1.030	.346	0.991
3 months	.581	1.588	.761	1.241	.511	1.413	.616	1.399
6 months	.610	1.666	.765	1.268	.503	1.481	.626	1.455
12 months	.614	1.525	.740	1.273	.460	1.412	.606	1.396
18 months	.613	1.510	.715	1.239	.419	1.461	.586	1.387
24 months	.622	1.457	.681	1.199	.388	1.311	.570	1.322
30 months	.627	1.362	.642	1.206	.330	1.177	.541	1.265
36 months	.627	1.414	.667	1.276	.364	1.362	.560	1.348

1. RR=TAM/Placebo

Table 6
Proportion of Women Reporting Vaginal Discharge in Tamoxifen Arm and Relative Risk Compared to Placebo Arm by Age Group and Examination

Examination	Age Group							
	35-49 yrs		50-59 yrs		> 60 yrs		Overall	
	TAM	RR[1]	TAM	RR[1]	TAM	RR[1]	TAM	RR[1]
Baseline	0.201	0.957	0.135	1.041	0.058	0.907	0.138	0.975
3 months	0.379	1.549	0.308	2.023	0.275	3.665	0.326	1.972
6 months	0.391	1.686	0.302	1.931	0.269	3.057	0.327	1.973
12 months	0.380	1.700	0.304	1.973	0.262	3.333	0.321	2.020
18 months	0.363	1.558	0.278	2.251	0.252	3.029	0.303	1.961
24 months	0.341	1.797	0.272	1.991	0.238	2.994	0.288	2.052
30 months	0.325	1.633	0.282	2.404	0.246	3.075	0.288	2.083
36 months	0.316	1.671	0.264	2.332	0.241	3.096	0.277	2.095

1. relative risk (rr)=Tam/Placebo

APPENDIX

e. Ganz PA, Day R, Costantino, JP.
Compliance with QoL Data Collection in NSABP BCPT

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COMPLIANCE WITH QUALITY OF LIFE DATA COLLECTION IN THE NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP) BREAST CANCER PREVENTION TRIAL

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SUMMARY

This paper describes compliance with the completion of a quality of life questionnaire in the Breast Cancer Prevention Trial, a large multi-centre randomized trial that is studying the efficacy of Tamoxifen in preventing breast cancer. In the first 4875 women enrolled in the control arm of the study, there was a very high rate of questionnaire completion at baseline, 3 months, 6 months and 12 months of follow-up (89·8 per cent completed forms at 12 months). The sample was examined according to demographic and risk factors, as well as by recruitment cohort. There was a significantly poorer compliance rate for the most recently recruited cohort that was followed-up during a time of substantial external negative publicity related to clinical trial research. Nevertheless, the overall compliance with completion of quality of life data in this trial is very high, which is probably attributable to the high educational status of the trial participants. © 1998 John Wiley & Sons, Ltd.

INTRODUCTION AND BACKGROUND

The Breast Cancer Prevention Trial (BCPT) is a large multi-centre chemoprevention trial designed to test the efficacy of the anti-oestrogen drug Tamoxifen in preventing breast cancer and coronary heart disease in healthy women at high risk for breast cancer. The study is being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) with funding primarily from the National Cancer Institute. The BCPT evolved from a series of prior studies that demonstrated the efficacy of Tamoxifen in the prevention of breast cancer systemic recurrence[1–4] and in the reduction of contralateral breast cancers in women with early stage breast cancer.[1–6] Based on the literature, other potential benefits of Tamoxifen include a decrease in cardiac events and osteoporotic fractures,[7–12] and these are secondary endpoints for the trial.

The BCPT uses a randomized, placebo-controlled trial design. The trial is being carried out at 119 nucleus clinical centres in the United States and Canada with many additional sub-centres.

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The original trial design planned to assign 8000 women to each arm of the trial (Tamoxifen/placebo), with all participants taking the study medication for five years after randomization. Recently, a re-evaluation of the breast cancer risk of participants enrolled in the trial, as well as participant compliance with therapy, has allowed a reduction in the target accrual to 13,000 participants total.

Potential medication side-effects may interfere with adherence to therapy in a prevention trial focusing on healthy individuals. Therefore, the leadership of the trial recognized the importance of collecting data on symptoms and quality of life as part of the BCPT, and developed a comprehensive battery of health-related quality of life (HRQL) instruments that are included in the regular assessment of participants at each clinical visit. The HRQL battery used in this study is described in detail elsewhere.[13] To summarize, it contained a total of 104 items which were constructed from the MOS-Short Form 36, the Centres for Epidemiological Studies-Depression Scale, a specially developed symptom checklist, and the Medical Outcomes Study Sexual Functioning Questionnaire. The BCPT represents the first major effort of the NSABP to include quality of life data collection in a group sponsored trial.

In an earlier report,[13] we found high rates of compliance with completion of the HRQL questionnaire at the baseline assessment. This paper examines longitudinal compliance with HRQL data collection during the course of the first 12 months after randomization, evaluating three successive cohorts of participants who were randomized to the placebo group during the first 18 months of the study. This represents a total sample size of $N = 4875$ at baseline, for whom HRQL data should be available at baseline and three subsequent assessments. As the trial is still masked to treatment assignment, this report includes data only from the placebo group. Examination of the control group alone eliminates any confounding of data compliance problems that could be related to potential drug toxicity. Use of the placebo control arm also allows estimation the minimum rate of missing HRQL data that can be attributed to staff error, participant unwillingness to respond, and other factors that may affect data quality.

METHODS

Sample Selection

Randomization of participants in the BCPT began on 1 July 1992 and was continued until the Spring of 1994, when all NSABP trials were temporarily closed to accrual because of investigations related to alleged data falsification in previous NSABP trials coming from one treatment institution in Canada. The BCPT did not begin accruing subjects actively again until November 1994. Although the earliest participants in the trial have now been on study for over 4 years, this report only examines the compliance performance for the first 12 months of HRQL data expected. If not received as of this reporting, these data would be considered permanently missing because of the elapsed time. Due to the double-masked design of the study, we had initially considered examination of compliance with HRQL data collection in all participants combined together. However, if the compliance rates were low, this might be attributed to an effect of the study medication. Therefore, to eliminate the confounding of a medication effect, this report examines the compliance in the placebo treatment group alone. At the time of trial unmasking, compliance with HRQL data collection in both the Tamoxifen and placebo treated groups will be determined to see if there are differences in compliance as a result of treatment.

Data collection and management

HRQL data were collected from the participants at each collaborating clinical centre using scannable, self-administered questionnaires. Although the questionnaires were supposed to be reviewed for completeness by the clinical centre staff prior to being forwarded to the NSABP Biostatistical Center at the University of Pittsburgh, we are uncertain whether this was routinely performed. In addition, participants were explicitly given the option of not responding to items on the questionnaire, and thus some missing data could be attributed to participant choice. At the Biostatistical Center, the questionnaires were first logged-in, then digitally scanned and electronically checked for missing, contradictory or impossible responses. If questionable responses were located, the data were placed in an electronic holding file and a query letter was sent to the collaborating centre in an attempt to resolve any issues. When all issues were resolved and data were acceptable, they were merged with the active study files for the BCPT.

Statistical Approach

The method of analysis in this paper is largely descriptive, emphasizing graphic and tabular presentations. The sample size is so large that any comparisons may yield statistically significant, but clinically unimportant findings. Nevertheless, this presentation represents the first examination of compliance with HRQL data collection in a prevention trial with healthy participants. Historically, in treatment trials, important problems with missing data have been identified, and we hypothesized similar problems in this study, especially given the relative length of the HRQL battery that was used.

RESULTS

Participant Demographic and Medical Characteristics

Between 1 July 1992 and 30 November 1993, 4875 women were assigned to the control group of the BCPT. These participants have been divided into three cohorts according to 6 month periods of randomization (cohort 1 = 1 July 1992 to 30 November 1992; cohort 2 = 1 December 1992 to 30 June 1993; cohort 3 = 1 July 1993 to 30 November 1993). The timeline for cohort randomization and 12 month follow-up data collection is illustrated in Figure 1. This subject recruitment time frame also corresponds to our early report on the baseline HRQL data on these participants.[13] Since recruitment occurred at a faster pace during the early part of the accrual period, cohort 1 has the largest number of participants ($N = 2250$, compared with $N = 1550$ in cohort 2 and $N = 1075$ in cohort 3). The demographic, social and breast cancer risk characteristics of each cohort were examined and there were no differences among them. As in our earlier report,[13] the trial participants are largely white (94·5 per cent), married (68·4 per cent), highly educated (78 per cent with more than a high school education), and have a substantial risk of breast cancer (49·3 per cent have $\geqslant 2{\cdot}81$ per cent 5 year risk of breast cancer).

Compliance with HRQL Data Collection

The BCPT uses an intent-to-treat analysis plan. Therefore, all participants are considered 'on study' if they have not withdrawn consent for active follow-up. Participants fall in this category, even if they no longer are 'on treatment', which is taking the study medication. Although HRQL

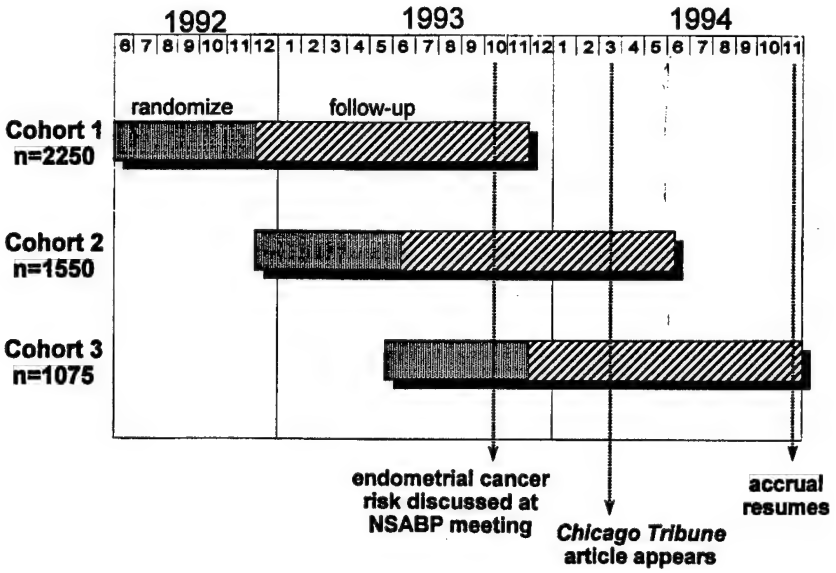

Figure 1. Timeline for accrual of three cohorts of participants recruited to the BCPT in the first 18 months after the trial was opened in July 1992. The timeline also notes several external events that may have affected recruitment and adherence

data are required of all participants remaining 'on treatment' specific instructions for follow-up in patients 'off treatment' has been less well-defined. Table I presents data on the number of participants *on study* at baseline, 3 months, 6 months and 12 months, as well as the number of participants still *on treatment*, and the number of participants who submitted a quality of life questionnaire (QLQ). These data are shown for the entire sample as well as by the three cohorts. While there is only a slight decline in the number of participants still *on study* at 12 months (99·9 per cent), only 92·4 per cent of placebo participants remain *on treatment* at 12 months. Overall, a QLQ was received for 89·8 per cent of the placebo group participants at the 12 month assessment, declining from 99·4 per cent at baseline. The number of placebo participants on treatment at 12 months, as well as the rate of QLQ submission at 12 months, varies by cohort, with cohort 3 having significantly fewer participants on treatment (chi square = 30·67, $p < 0·001$) and significantly fewer with submitted QLQ forms (chi square = 49·23, $p < 0·001$).

We also examined the rate of completed QLQ forms according to selected demographic and risk characteristics (Table II). There was no relationship between form completion and age, ethnicity, education, income or breast cancer risk. These same characteristics were examined within each cohort (data not shown), and no relationship was observed in these three subgroups. Clinical centre characteristics were hypothesized to play a possible role in data quality. Therefore, we examined low, intermediate and high volume clinical centres ($\leqslant 50$ participants, 51–59 participants, $\geqslant 100$ participants), proposing that low and high volume centres potentially would have more difficulty, but for different reasons. As seen in Table II, the intermediate volume centres tended to have the highest rates of QLQ form submission at each of the time points after baseline, with chi-square tests being significant ($p < 0·04$) at each of the follow-up assessments.

Table I. Adherence measures for the BCPT placebo group by examination and six-month randomization cohorts

Adherence measure	Baseline	3 months	6 months	12 months
Participants on study				
cohort 1	2250 (100·0)	2249 (99·6)	2245 (99·8)	2248 (99·9)
cohort 2	1550 (100·0)	1549 (99·9)	1549 (99·9)	1548 (99·9)
cohort 3	1075 (100·0)	1075 (100·0)	1074 (99·9)	1075 (100·0)
Overall	4875 (100·0)	4873 (99·9)	4868 (99·9)	4871 (99·9)
Participants on treatment				
cohort 1	2227 (99·0)	2203 (97·9)	2162 (96·1)	2119 (94·2)
cohort 2	1536 (99·1)	1525 (98·4)	1492 (96·3)	1433 (92·5)
cohort 3	1070 (99·5)	1058 (98·4)	1016 (94·5)	954 (88·7)
Overall	4833 (99·1)	4786 (98·2)	4670 (95·8)	4506 (92·4)
Participants completing QLQ				
cohort 1	2244 (99·7)	2071 (92·0)	2092 (93·0)	2063 (91·7)
cohort 2	1537 (99·2)	1437 (92·7)	1446 (93·3)	1410 (91·0)
cohort 3	1066 (99·2)	1027 (95·5)	989 (92·0)	904 (84·1)
Overall	4847 (99·4)	4535 (93·0)	4527 (92·9)	4377 (89·8)

For the next level of analysis, we examined the rates of missing data items for each of the instruments in the QLQ. As can be seen in Table III, there was no systematic evidence of missing data in any of the individual instruments. Response rates to the sexual functioning questionnaire, an area that was thought to be quite sensitive, were just as high as for the other instruments. Importantly, while the rates of submitted forms declined somewhat between baseline and 12 months (Table II), the number of missing items did not change from administration to administration. This suggests that if the participant had a submitted form, it had a high likelihood of being completed. We did note difficulty with the response format of the symptom checklist (SCL). Respondents were asked to indicate whether they had a symptom with 'yes' or 'no', referred to here as the binary SCL. If the response was 'yes', then they were requested to rate the severity of the symptoms from 0 to 4. Therefore, not all participants were expected to respond to the multiple SCL response items. However, some respondents did not understand the format and some severity data are missing as a result. We also examined the completion rates by cohort (data not shown), and they are similar to those reported in Table III.

Figure 2 summarizes the overall data flow for the HRQL data in the placebo group during first 12 months on study. While there is about a 10 per cent decline in the number of submitted QLQ forms between baseline and the 12 month assessment, the rates of complete data within the QLQ remain constant across all four assessments. Figure 3 presents the cumulative number of forms submitted overall and by cohort. Overall, 84·3 per cent of the 4875 participants who were assigned to placebo submitted all four QLQ forms. Cohorts 1 and 2 have similar rates of having all four forms completed, while this is somewhat lower in cohort 3. However, more than 90 per cent of all participants had at least three QLQ forms submitted during the first year on study.

Table II. BCPT participants in the placebo group completing the quality of life questionnaire (QLQ) by examination and selected demographic characteristics

Demographic characteristic	Baseline	3 months	6 months	12 months
Age				
35–49 yrs	1912 (99·3)	1783 (92·6)	1793 (93·1)	1723 (89·5)
50–59 yrs	1490 (99·3)	1400 (93·3)	1386 (92·4)	1353 (90·2)
60–79 yrs	1445 (99·7)	1352 (93·2)	1348 (93·0)	1301 (89·7)
Ethnicity				
white	4591 (99·6)	4315 (93·6)	4312 (93·6)	4172 (90·5)
non-white	189 (100·0)	170 (90·0)	166 (87·8)	157 (83·1)
unknown	67 (87·0)	50 (64·9)	49 (63·6)	48 (62·3)
Education				
⩽high school	1117 (100·0)	1033 (92·5)	1038 (92·9)	1005 (90·0)
vocational or some college	1526 (99·5)	1448 (94·5)	1429 (93·2)	1363 (88·9)
college degree	899 (99·6)	842 (93·2)	843 (93·4)	818 (90·6)
post-graduate training	1238 (99·4)	1162 (93·3)	1168 (93·8)	1143 (91·8)
unknown	67 (87·0)	50 (64·9)	49 (63·6)	48 (62·3)
Income				
⩽ 24,999	996 (99·8)	950 (95·2)	948 (95·0)	907 (90·9)
25,000–49,999	1453 (99·6)	1383 (94·8)	1387 (95·1)	1338 (91·7)
50,000–99,999	1484 (99·5)	1432 (96·0)	1423 (95·4)	1379 (92·4)
⩾ 100,000	513 (99·6)	491 (95·3)	489 (95·0)	483 (93·8)
unknown	401 (97·6)	279 (67·9)	280 (68·1)	270 (65·7)
Relative Risk				
⩽ 3·00	1165 (99·7)	1081 (92·5)	1078 (92·2)	1034 (88·5)
3·01–5·00	1810 (99·1)	1702 (93·2)	1701 (93·2)	1654 (90·6)
⩾ 5·01	1872 (99·6)	1752 (93·2)	1748 (93·0)	1689 (89·8)
5-year probability				
⩽ 2·00	1147 (99·2)	1080 (93·4)	1069 (92·5)	1021 (88·3)
2·01–2·80	1310 (99·5)	1206 (91·6)	1218 (92·5)	1182 (89·8)
2·81–4·00	1172 (99·4)	1097 (93·0)	1112 (94·3)	1073 (91·0)
⩾ 4·01	1218 (99·6)	1152 (94·2)	1128 (92·2)	1101 (90·0)
Center by Accrual				
⩽ 50 participants	564 (99·3)	503 (88·6)	523 (92·1)	488 (85·9)
51–99 participants	1704 (99·5)	1626 (94·9)	1613 (94·2)	1560 (91·1)
⩾ 100 participants	2597 (99·4)	2406 (92·8)	2391 (92·2)	2594 (89·8)

DISCUSSION

To the best of our knowledge, this paper represents the first report of compliance with longitudinal HRQL data collection in a cancer chemoprevention trial. The sample size is large, and includes the number of expected and received forms for baseline and three follow-up assessments during a 12 month period of data collection. In addition, the sample is examined according to three separate recruitment cohorts over an 18 month period of time. This latter aspect of the report allows comparison of the initial study volunteers who might be most compliant to those

Table III. Instrument and overall QLQ completion statistics for BCPT control group participants submitting a quality of life questionnaire at each examination

Instrument	Baseline $n = 4847$	3 months $n = 4535$	6 months $n = 4527$	12 months $n = 4377$
CES-D (20 items)				
number completed (%)	4704 (97·0)	4402 (97·1)	4394 (97·1)	4273 (97·6)
mean items completed (SE)	19·9 (0·01)	19·9 (0·01)	19·9 (0·01)	19·9 (0·01)
median items completed (range)	20·0 (0–20)	20·0 (0–20)	20·0 (0–20)	20·0 (0–20)
Binary SCL (42/43 items)				
number completed (%)	4500 (92·8)	4270 (94·1)	4311 (95·2)	4165 (95·2)
mean items completed (SE)	42·1 (0·02)	42·1 (0·03)	42·2 (0·02)	42·2 (0·02)
median items completed (range)	42·0 (1–43)	42 (1–43)	42·0 (1–43)	42·0 (1–43)
Multiple SCL (42/43 items)*				
number completed (%)	449 (9·3)	641 (14·1)	651 (14·4)	676 (15·4)
mean items completed (SE)	12·4 (0·17)	15·0 (0·20)	15·2 (0·20)	15·8 (0·21)
median items completed (range)	9·0 (0–43)	10·0 (0–43)	10·0 (0–43)	11·0 (0–43)
SF-36 (36 items)				
number completed (%)	4112 (94·0)	4221 (93·1)	4225 (93·3)	4112 (94·0)
mean items completed (SE)	35·9 (0·01)	35·8 (0·02)	35·9 (0·02)	35·9 (0·01)
median items completed (range)	36·0 (0–36)	36·0 (0–36)	36·0 (0–36)	36·0 (0–36)
MOS-Sex (5 items)				
number completed (%)	4594 (94·8)	4278 (94·3)	4266 (94·2)	4134 (94·5)
mean items completed (SE)	4·8 (0·01)	4·8 (0·02)	4·8 (0·02)	4·8 (0·02)
median items completed (range)	5·0 (0–5)	5·0 (0–5)	5·0 (0–5)	5·0 (0–5)
QLQ overall (103/104 items)				
number completed (%)	3842 (79·3)	3694 (81·5)	3722 (82·2)	3659 (83·6)
mean items completed (SE)	102·7 (0·04)	102·7 (0·07)	102·7 (0·05)	102·8 (0·04)
median items completed (range)	103·0 (1–104)	103·0 (1–104)	103·0 (1–104)	103·0 (1–104)
QLQ overall (145/147 items)*				
number completed (%)	399 (8·2)	564 (12·4)	564 (12·5)	610 (13·9)
mean items completed (SE)	115·1 (0·18)	117·6 (0·22)	118·0 (0·21)	118·7 (0·22)
median items completed (range)	111·0 (1–147)	113·0 (1–147)	113·0 (1–147)	114·0 (1–147)

* Includes the severity ratings on the symptom checklist

who entered later. Using this approach, we are also able to gauge the effects of the extraordinary external events that occurred in the spring of 1994 that were likely to affect recruitment and adherence in this trial.

In reviewing the analyses presented here, we were extremely pleased and surprised to find the high rates of compliance with QLQ form submission, as well as the low rates of missing items on each of the QLQ scales. The stability of the number of missing items across all four assessments, and among all three cohorts of participants, indicates that the QLQ was highly acceptable and that the occurrence of missing responses was likely to be random. While this finding may indicate an unwillingness of some participants to answer certain items, it may also indicate staff error in checking the QLQ for completion before collection from the participant. Unfortunately, we cannot estimate the number of missing items due to each factor. However, most of the scales used

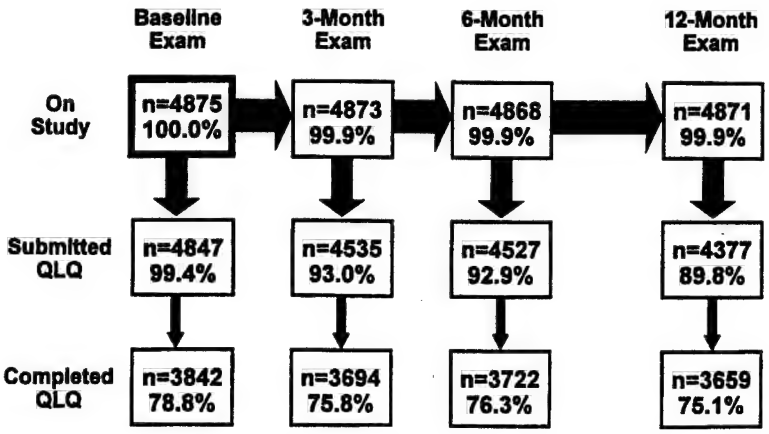

Figure 2. Summary of overall data flow with number of placebo participants on study (number of expected assessments), with the number of submitted forms, and number of forms without missing data. All percentages are calculated based on the total number of control participants randomized 1 June 1992 to 30 November 1993 ($n = 4875$)

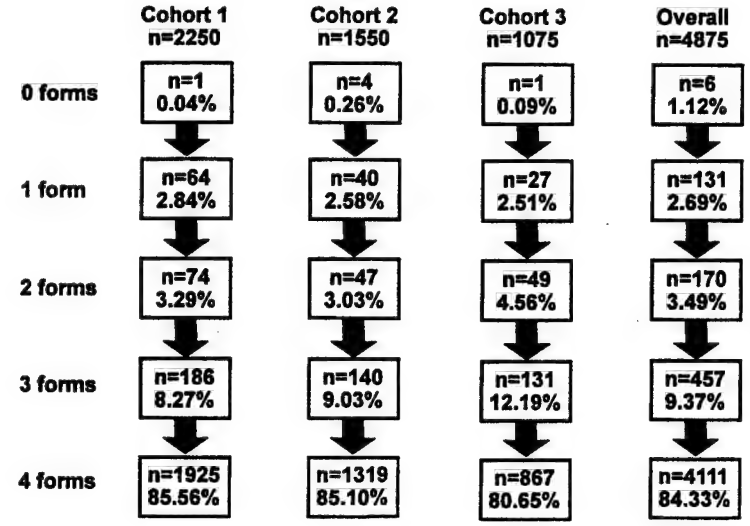

Figure 3. Cumulative number of QLQ forms received overall and according to randomization cohort

in our HRQL battery can still be scored successfully even with 1 or 2 missing items (for example, the MOS SF-36), therefore the data loss from occasional missing items may be less significant than indicated by the absolute number of missing items.

The drop-off in QLQ submissions from cohort 1 and 2 to cohort 3 most likely reflects the external events of the spring of 1994, since cohort 3 was most affected by this (see Figure 1). Examination of future participants recruited after that time period should allow clarification of this issue. Even so, the compliance rates, in terms of QLQ form submission are very high, with

overall compliance of nearly 90 per cent of the expected forms being submitted for the 12 month assessment. This rate of HRQL data loss is probably the minimum rate one might expect, given that these participants were on placebo, and were not affected by medication toxicity that might further reduce compliance through participants going off study or being unwilling to complete the form. Future examination of compliance with HRQL data collection in the Tamoxifen treatment arm will permit estimation of the additional effect of treatment on compliance with data collection.

Interestingly, we found no relationship between various demographic, social or risk factors in these study participants and the rates of compliance with HRQL data collection. On first glance, this may be surprising; however, it is likely that the high socio-economic status of these participants (excellent reading ability, familiarity with questionnaires, high motivation for participation in the study), made our task easier. Another relevant observation is that this trial was begun at a time when clinicians and data managers were becoming increasingly familiar with the idea of the assessment of HRQL in clinical trials. Thus, this data collection was not perceived as burdensome, especially since the well-educated participants had little difficulty completing the forms. In addition, since the study participants were healthy, the questionnaires did not present as much of a hardship for them to complete as might be the case in cancer treatment trials involving patients with advanced metastatic cancer.[14]

In the future, the HRQL compliance data we have reported here in the placebo group of the BCPT will provide a minimum estimate of missing data for sample size and power calculations when quality of life is a major trial endpoint. Although these high rates of compliance may not be sustained throughout the five years of the study, our initial results are encouraging. Our analyses also suggest some trends in data quality that may reflect particular site characteristics (for example number of participants accrued). Low accruing sites may not have the volume of participants to be systematic in their procedures and data collection, whereas, high accruing sites may be understaffed and overburdened, and therefore may overlook the HRQL data collection with greater frequency. These findings can help in counselling clinical centres that may be at risk for incompelete HRQL data collection. Finally, as a result of these analyses, we have identified a constant rate of missing items from our QLQ, which could be related to patient refusal or staff omission. We will plan to address this problem through education of our data co-ordinators and clinical investigators to check all forms for completeness prior to submission to eliminate unintentional omission of responses. Future analyses will evaluate whether we can improve upon this rate of missing items from our QLQ form.

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APPENDIX

f. B-23 HRQL Protocol (Instruments at Rear)

NSABP B-23 QOL

A STUDY TO EVALUATE THE EFFECT ON QUALITY OF LIFE OF ADRIAMYCIN CYCLOPHOSPHAMIDE (AC) THERAPY VERSUS CYCLOPHOSPHAMIDE, METHOTREXATE, AND 5-FLUOROURACIL (CMF) THERAPY IN WOMEN WITH AXILLARY NODE-NEGATIVE, ESTROGEN-RECEPTOR-NEGATIVE, PRIMARY INVASIVE BREAST CANCER BEING TREATED ON NSABP B-23

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Final Version as of April 16, 1997 (PLEASE DESTROY ALL OTHER VERSIONS)

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1.0 BACKGROUND

The evaluation of new cancer therapies has traditionally included response to treatment, toxicity, disease-free survival (DFS) and overall survival (S). Over the past two decades, there has been a growing interest in quality of life (QOL) as another potentially useful endpoint.[1,2] QOL endpoints have been included in many trials conducted by the cooperative clinical trials groups and are recognized (along with other endpoints) as a basis for new drug approval by the FDA.[3] Adjuvant therapy for breast cancer has been identified as one of several current areas of cancer treatment research in which QOL endpoints would be most important.[3]

Although QOL is a relatively new area of research, it is generally accepted that the subjective nature of QOL mandates that the patient define it and that it be measured and expressed in terms of issues that are of direct importance to the patient.[4] Slevin et al demonstrated the discrepancy between the perception of QOL when rated by the outside observer versus the patient, showing a poor correlation between these ratings.[5] While toxicity ratings done by health professionals provide clinically important information, they cannot be used as a substitute for a comprehensive description of side effects from the patient's point of view.[6] There is also agreement among QOL researchers that the concept of QOL is multidimensional. The components considered central to this concept include physical functioning (e.g., mobility, self-care), disease and treatment-related symptoms, psychological functioning (e.g., depression, anxiety), and social functioning (e.g., family interaction, work, recreation).[1,7] Additional components that may be considered are sexual function, satisfaction with health care, and existential and spiritual concerns.[1]

A number of validated questionnaires are available to measure QOL in cancer patients; these instruments can be classified into generic measures of health status, cancer- and site-specific measures, symptom checklists, and global QOL measures.[7] The choice of a particular tool should be dictated by the goals of the assessment, study population, type of intervention, and resources available for data collection.[7]

The role of QOL assessment in a given trial depends on the primary aim and the results of the study. In studies in which the primary aim is to improve DFS and overall S by adding another drug to a standard regimen or by increasing the dose (usually at the expense of increased toxicity), QOL is usually considered a secondary endpoint.[6] However, QOL assessment can be helpful in weighing the risks and benefits of treatment options, particularly when differences in DFS and S among the options are small. In such situations, a comparison of quality-adjusted S rates between the treatment arms may facilitate therapeutic decisions. Information on QOL is especially important in clinical decision-making when treatments are associated with similar S but different toxicities.[3,6] In fact, in many clinical trials, the main objective is to show that a treatment which offers a better QOL (e.g., is less toxic, shorter, or better in some other respect) is as effective as the standard regimen. In those trials, QOL should be regarded as a primary endpoint.

2.0 RATIONALE FOR UNDERTAKING THE STUDY

NSABP B-23 compares the efficacy of four courses of doxorubicin (Adriamycin) and cyclophosphamide (AC) with six courses of standard cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) and the efficacy of tamoxifen versus placebo in each chemotherapy group in women with node-negative, estrogen-receptor (ER)-negative breast cancer. In addition to chemotherapy, lumpectomy patients receive radiation therapy to the breast.

Patients assigned to CMF receive six cycles of chemotherapy. The duration of each cycle is 28 days. Cyclophosphamide 100 mg/m^2 p.o., q.d. is given on days 1 through 14 of each cycle. Methotrexate 40 mg/m^2 i.v. is given on day 1 and day 8 of each cycle. 5-fluorouracil 600 mg/m^2 i.v. is given on day 1 and day 8 of each cycle. Tamoxifen 10 mg p.o., b.i.d., or placebo, begins on day 1 of cycle 1 of chemotherapy and is given for 5 years.

Patients assigned to AC receive four cycles of chemotherapy. The duration of each cycle is 21 days. Doxorubicin (Adriamycin) 60 mg/m^2 and cyclophosphamide 600 mg/m^2 are given intravenously on day 1 of each cycle. Tamoxifen 10 mg p.o., b.i.d., or placebo, begins on day 1 of cycle 1 of chemotherapy and is given for 5 years.

The primary aims of NSABP B-23 are 1) to determine whether administering four cycles of AC is superior to six cycles of CMF, and 2) to determine whether tamoxifen added to AC or to CMF alone is more efficacious than AC or CMF alone.

NSABP B-23 offers an excellent opportunity to assess the impact on patients' QOL of specific therapies including short-term effects of two different chemotherapy regimens and potentially, the longer-term effects of tamoxifen therapy (through one year of treatment) on patients with stage I breast cancer. The trial provides an opportunity to observe these effects on women who have a relatively good prognosis, are free of symptoms related to the disease, and who comprise a homogenous group of patients already being controlled for in terms of disease state and baseline functional status. Demographic and clinical data retrieval are already required by the primary study.

Prior experience from the NSABP B-15 study in patients with positive axillary nodes who were 49 years of age or younger, or 50 - 59 years of age and progesterone-receptor (PR)-negative, suggests that AC and CMF are equivalent in terms of efficacy.[8] If NSABP B-23 has a similar result, QOL considerations may have primary importance in guiding the selection between these two therapeutic strategies. Although standard assessment of adverse drug reactions and the difference between the two regimens in the duration of chemotherapy provide some indication of the potential impact of each treatment on QOL, it is essential that QOL be assessed from the patient's point of view. In addition, because one-half of the patients are taking tamoxifen, this study may provide a chance to capture information relative to the influence of long-term tamoxifen therapy on QOL. The double-blind design (tamoxifen vs. placebo) will strengthen the validity of results in this regard.

3.0 SPECIFIC AIMS

3.1 Primary Aim

The primary aim of this study is to compare QOL in women with primary breast cancer treated with one of two adjuvant chemotherapy regimens: Adriamycin and cyclophosphamide (AC), or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) as described in Section 2.0.

3.2 Secondary Aims

The secondary aims of this study are to investigate the effect of local treatment (mastectomy versus lumpectomy and radiation therapy) and the effect of tamoxifen therapy on QOL in women with primary breast cancer.

4.0 PATIENT ELIGIBILITY

The QOL study will be conducted at institutions participating in NSABP B-23. This includes NSABP CCOPs and non-CCOP institutions. All patients newly entered into B-23 will be asked to participate in the B-23 QOL study.

Patients entering the B-23 QOL study must also speak English, French, or Spanish and must sign a QOL study consent form. It should be emphasized that refusal to participate in the QOL study will have no effect on the patient's participation in the B-23 treatment trial.

5.0 INSTRUMENTS

The following measures were incorporated into the B-23 QOL Questionnaire (Appendix A) to obtain a comprehensive assessment of QOL:

- Functional Assessment of Cancer Therapy (FACT-B)
- Symptom Checklist
- QOL Rating Scale
- Vitality Scale
- Three additional QOL questions pertaining to (1) general health perceptions, (2) physical limitations, and (3) return to normal activity.

5.1 FACT-B

This questionnaire is a multidimensional, 44-item, cancer-oriented measure of QOL developed by David Cella.[9] Five subscales provide scores for physical well-being, social/family well-being, relationship with the physician, emotional well-being, and functional well-being. Nine additional questions refer to problems commonly experienced by women with breast cancer. Although this scale is relatively new, it has been extensively validated and is rapidly gaining acceptance among QOL researchers. Spanish and French translations are available.

5.2 Symptom Checklist (SCL)

None of the published symptom checklists has been designed specifically for patients with early-stage breast cancer. The most comprehensive is the Rotterdam Symptom Checklist (RSCL),[10] which includes 34 items. However, the scale is relatively long and does not include symptoms related to local treatment for breast cancer or symptoms commonly associated with hormonal therapy. The Breast Cancer Chemotherapy Questionnaire[11] includes a number of symptoms commonly seen in patients undergoing adjuvant therapy. However, it has the same drawbacks as the RSCL. In addition, it appears somewhat redundant and overlaps with the FACT-B scale.

Given the importance of physical symptoms in evaluating the impact of chemotherapy on QOL, we have decided to select the most relevant items from several existing instruments, including the Breast Cancer Prevention Trial QOL Questionnaire. The symptoms have been selected based on a review of the literature, on NSABP toxicity data, and on consultations with clinicians and experts on QOL assessment. The NSABP B-23 SCL includes 17 symptoms commonly reported by patients with cancer, especially those undergoing surgery and radiotherapy for breast cancer, standard chemotherapy, and hormonal therapy (tamoxifen). Although the list as a whole has not been formally validated, the individual items have been tested.

Initially, each symptom will be scored on a 5-point Likert scale and analyzed individually. Three overall measures of "symptom burden" will be calculated for each patient: 1) the sum of all item scores; 2) number of symptoms reported; and 3) the highest score reported on any item. The summary measures will be used in the analysis only after testing their validity and reliability.

The SCL has been developed in a way that ensures content and face validity. Construct validity will be evaluated by correlations with other measures of quality of life, especially the FACT-B and its components, and with adverse drug reactions assessed according to the NCI criteria. We will also compare the scores while on chemotherapy for patients who subsequently dropped out of the trial with the rest of the sample (predictive validity). To assess the internal consistency of the SCL, we will analyze the inter-item correlation matrix and calculate the Cronbach's alpha coefficient. Test-retest reliability will be tested in a selected group of patients whose overall quality of life has not changed between two consecutive assessments. Finally, the responsiveness of the SCL will be compared to that of the FACT-B and its components.

5.3 QOL Rating Scale

This scale will evaluate the patient's overall perception of QOL on a scale from 0 to 10. The assessment will provide a single QOL coefficient (0-1) for the purpose of "utility" estimation. This will facilitate the calculation of quality-adjusted survival for the two chemotherapy treatment groups. In addition, it will enable us to study the correlation of the overall assessment of QOL with scores obtained from multidimensional instruments, and with symptom severity.

5.4 Vitality Scale

This four-item scale is part of the MOS SF-36 questionnaire,[12] a widely used generic measure of health status. The scale may be useful in detecting common but less specific side effects of cancer therapy, such as fatigue and lack of energy. These diffuse reactions are difficult to capture by the remaining measures.

5.5 Additional QOL Items

Some important aspects of health-related quality of life are not adequately ascertained by the above instruments. These aspects include (1) general perceptions of health, (2) limitations in daily physical activity, and (3) extent to which the patient is able to resume normal activities. To measure the first two domains, we will use validated questions derived from the MOS instrument.[13]

Return to normal activities will be measured by a question developed by D. Cella[14] (see item #63, Baseline and Follow-Up and item #62 Treatment, Appendix A).

5.6 Wording of Instructions

QOL questions should refer to an appropriate period of time before (and including) the day of assessment. This recall period will be different for the baseline and follow-up assessments, as compared with the assessments while on chemotherapy. The former will refer to "the last 7 days," as in the original FACT-B scale, whereas the latter will refer to the period "since the last treatment." This modification has been introduced to capture the QOL during each cycle of chemotherapy in both treatment arms and has been approved by the author of the FACT-B scale.[9] The recall period will be the same for each component of the QOL questionnaire except the single item on general health perceptions (see item #2, Baseline and Follow-Up, Appendix A).

6.0 DATA COLLECTION

The QOL assessment schedule for B-23 is given in Table 1. Each patient will be evaluated at baseline, during chemotherapy, and after the completion of chemotherapy. The timing of the administration of the QOL instrument in this study is complicated by the differences in the chemotherapy schedules of the AC versus CMF regimens, which differ in their duration and total number of cycles. In addition, the timing of the radiation therapy for patients who have had a lumpectomy is different in patients treated with AC versus CMF. The timing of the QOL assessment schedule for each group has been adjusted in an attempt to capture comparable information in each chemotherapy group. Thus, the total number of QOL data points, and the intervals between consecutive assessments, will not be the same for patients receiving AC vs. CMF; however, the proposed schedule provides for a fair comparison between the arms. Multiple measurements on each patient will increase precision (by reducing random errors) and facilitate the analysis of changes in QOL over time. To minimize the burden on the patient and staff, while, at the same time, ensuring high quality of the data, the questionnaire will be self-administered under the supervision of a nurse/data coordinator.

Table 1. B-23 QOL Assessment Schedule

CHEMOTHERAPY REGIMEN	BASELINE	DURING CHEMOTHERAPY	INTERIM	FOLLOW-UP		
AC	Day 1 of Course 1 before chemotherapy administration	Day 1 of courses 2 through 4 before chemotherapy administration.	Week 18	Week 26 (6 month follow-up)	Week 39 (9 month follow-up)	Week 52 (1 year follow-up)
CMF	Day 1 of Course 1 before chemotherapy administration	Day 1 of courses 2 through 6 before chemotherapy administration.	Week 30*		Week 39 (9 month follow-up)	Week 52 (1 year follow-up)

*will be completed only in the CMF mastectomy group

For questions about the schedule of QOL assessments when treatment is delayed, call the NSABP Clinical Coordinating Section at 1-800-477-7227.

6.1 Baseline Assessment (Questionnaire Version A)

To avoid any potential interference with accrual to NSABP B-23, only women who have been randomized will be asked to participate in the QOL study. (see Section 4.0) Thus, baseline assessment can be done any time between randomization and initiation of therapy, including on day 1 of cycle 1. The reasons patients decline to participate in the B-23 QOL study will also be collected, and demographic data from these patients will be analyzed separately to address the issue of representativeness of study participants.

6.2 Assessments During Chemotherapy (Questionnaire Version B)

While patients are on chemotherapy, QOL assessments will be performed in the clinic, before treatment. Questionnaires will be administered in both groups on day 1 of each cycle of chemotherapy. Should a chemotherapy dose be delayed (for any reason), QOL assessment will also be delayed. If there are no delays, patients in the AC group will be evaluated every 3 weeks, and patients in the CMF group, every 4 weeks. An exception to this schedule will occur in patients receiving CMF who have had a lumpectomy. These patients will undergo radiation therapy after the first course of CMF. The second cycle of CMF will be delayed until the completion of radiation therapy and recovery from any associated hematologic toxicity. Hence, the assessment done before cycle 2 will be useful in ascertaining the effect of breast irradiation on QOL. For patients who have had a lumpectomy and are randomized to AC, radiation therapy will be given after the completion of AC therapy and recovery from any hematologic toxicity (usually no later than 4 weeks post-chemotherapy). The effect of radiation therapy on the QOL in these patients will be reflected in the 18-week follow-up assessment (see Section 6.3).

6.3 Follow-Up Assessments (Questionnaire Version A)

Given the primary objective of this study, it will be crucial to capture the changes in patients' assessment of QOL as they are recovering from many of the short-term effects of their chemotherapy regimen (i.e., returning toward their baseline QOL). To this end, an interim follow-up assessment will be performed on week 18 in the AC group and week 30 in the CMF group, i.e., 6 weeks after the end of the last cycle of chemotherapy. However, interim assessments will not be performed in the CMF lumpectomy group (since the radiation therapy will delay chemotherapy cycles 2 through 6 by at least 5 weeks) or in patients whose last dose of chemotherapy has been delayed by 4 weeks due to prior toxicity. In the AC-lumpectomy group, the interim assessment will help evaluate the effect of radiation therapy on QOL. Because no follow-up visit is scheduled at week 18 or week 30, the questionnaire will be mailed to all participants. To ensure a high response rate, the mailing will be followed within 2 weeks by a telephone call to non-respondents. Patients who have not returned the questionnaire will be asked to complete it over the telephone.

Subsequent to the interim follow-ups, QOL data will be obtained at the time of routine follow-up visits during the first year on study, i.e., at 6, 9, and 12 months in the AC group and at 9 and 12 months in the CMF group. These assessments will help determine whether patients have returned to, or possibly exceeded, their "baseline" QOL assessment. (Note: The baseline QOL assessment is performed following the breast cancer diagnosis and primary surgery [See Section 6.1].)

7.0 DATA ANALYSIS

The current protocol is designed to assess the participant QOL at baseline, during treatment, and in the recovery period for the two chemotherapy arms (AC vs. CMF) of the B-23 clinical trial. Routine assessments will be carried out on entry into the trial; at the beginning of each treatment cycle; and, depending on treatment, at three or four points after the completion of therapy. The most difficult statistical aspects of this study arise from the fact that the length of the treatment cycles, the timing of secondary treatment modalities (i.e., radiation), and the length of the entire treatment period vary between the trial arms. Additional problems also arise from the possibility of treatment delays due to toxicities and the creation of outcome biases due to differential withdrawal rates from the two arms.

7.1 Hypotheses

Statistical methods to be used in the study will be reviewed under the heading of four a priori hypotheses to be tested:

Hypothesis 1 Women randomized to the AC and CMF arms of the trial will show similar baseline levels of QOL. That is, recent surgical procedures (i.e., lumpectomy vs. mastectomy) experienced by the study participants will not have a differential effect on baseline QOL scores.

Hypothesis 2 After the initiation of chemotherapy (i.e., AC or CMF), women in both arms of the trial will show a statistically significant and similar decline in their QOL, which will last until the completion of their course of treatment.

Hypothesis 3 After the completion of treatment, women in both arms of the trial will show a similar recovery to baseline levels of QOL over the succeeding 6-month period.

Hypothesis 4 Over the 12-month period encompassed by this study, the only differences between the treatment arms relative to baseline QOL measurements will be in the total amount of time spent with depressed levels of QOL, rather than in the absolute levels of the observed decline. This hypothesis will also be tested using "quality-adjusted" time on study, where the quality adjustment represents a simple weighting of the time on study by scores on the different instrument scales. The hypothesis is that patients in the AC arm will have a significantly higher quality-adjusted time on study compared to patients in the CMF arm.

7.2 Methods of Analysis

Given the nature of the data in this protocol and the methodological constraints they impose, graphical methods of analysis will play a particularly important role and will be supplemented by univariate and multivariate analysis of variance procedures.

Hypothesis 1: Baseline levels of QOL for the women receiving lumpectomy and mastectomy will be described using means, standard deviations and standard errors, medians, and ranges for each of the component scales in the questionnaire. Simple hypothesis tests between the two groups may be carried out using parametric one-way analysis of variance or nonparametric equivalents, such as the Kruskal-Wallis test. The significance of potential covariates, such as participant age, for QOL levels may be tested through inclusion in the ANOVA design.

Hypothesis 2: This hypothesis will be tested using formal methods of statistical inference and graphical techniques. For both the AC and CMF arms of the trial, mean and median levels of QOL as measured by the different component scales of the questionnaire will be plotted for each treatment cycle. Ninety-five percent confidence intervals will be calculated and included on the plots. It is expected that these plots will visually indicate that:

- a statistically significant decrease occurs in the QOL of the women in both chemotherapy arms after the initiation of treatment; and,

- despite some temporal fluctuations in QOL throughout the treatment period, both chemotherapy arms remain similarly depressed throughout the full course of treatment.

This graphical approach will be supplemented by the use of repeated measures of analysis of variance. It is expected that these analyses will show main effects for time (e.g., baseline levels relative to treatment levels) but no main effects for treatment group. The data points used in the repeated measures procedures will refer to treatment cycles rather than to absolute time on treatment. There are also certain cycles of treatment that cannot be compared between the two chemotherapy arms (e.g., cycles 5 and 6 of the CMF groups).

Hypothesis 3: This hypothesis will also rely primarily upon graphical methods to compare the two chemotherapy arms. Mean and median QOL levels in both chemotherapy arms, along with 95% confidence intervals, will be calculated and plotted for the interim and follow-up assessments. Besides univariate comparisons of QOL levels at specific time points (e.g., 9 months and 1 year), the interim and follow-up examination dates have been chosen in order to permit the investigators to make quantitative comparisons of the rate and pattern of

recovery towards baseline levels of QOL in the different chemotherapy arms. In this regard, the interim assessment permits a measurement of QOL within approximately 6 weeks of the completion of the last treatment cycle in both study arms. Using these data, linear estimates can be calculated for the mean time required for participants to reach a given percentage of baseline QOL (e.g., 80%) for each arm. The differences between the chemotherapy arms in these estimates and the effects of covariates like age can be tested using parametric and nonparametric analysis of variance techniques.

Hypothesis 4: The estimated number of days with a depressed QOL relative to baseline (e.g., <80% of baseline) and quality-adjusted time on study for the patients in each treatment arm will be summarized using means, standard deviations, medians, and ranges. The former measure will automatically adjust for any baseline differences due to initial surgical procedures (e.g., lumpectomy or mastectomy), while the latter measure will adjust for differential baselines. The statistical significance of differences across the arms can be tested using parametric and nonparametric analysis of variance methods.

7.3 Missing Data

Missing data may occur for at least three reasons:

- the participant refuses to fill out the questionnaire, or the staff at the institution fails to ask the participant to complete the questionnaire;
- the intended date for completion of the questionnaire is missed due to treatment delays resulting from drug toxicities or the side effects of radiation therapy; or
- the participant has decided to withdraw from the treatment trial.

One of the main reasons for performing a QOL examination each time a woman appears for treatment is to avoid missing data. An alternative is to perform fewer examinations at more widely spaced periods. This is problematic because there are no common time points at which all of the arms are simultaneously examined and because of the risk of missing data resulting from complex QOL assessment scheduling problems. The emphasis on graphical methods of analysis also tends to minimize the effects of participants who refuse to complete the questionnaire or miss assessment points for other reasons.

The second and third reasons for missing data are particularly important because they can lead to biased findings. It may be that participants with the worst quality of life have the most treatment delays or withdraw most often from the study. Thus, a missing data mechanism may exist whereby the patients' censoring mechanism is related to the outcome.[15] If these data are simply handled as

"missing at random," they may lead to an underestimate of the true mean (or median) levels of decline in QOL due to chemotherapy. Moreover, if there is an imbalance between the chemotherapy arms in numbers of withdrawals and treatment delays because of significantly different levels of toxicity, the result may be that the survivors in the arm with the highest level of toxicity actually have higher mean levels of QOL when compared to the survivors in the other arm. In effect, all the participants with the poorest QOL have quit the trial or had their treatment delayed.

Because of possible biases in comparing QOL scores in the AC therapy versus the CMF therapy groups, the following analytical techniques will be used to detect a missing value mechanism:

- Proportions of missing data in the AC arms versus CMF arms will be compared at each scheduled measurement time. The significance levels of the comparison will be assessed using simple tests of binomial proportions.

- If one or both of the arms have a large dropoff in QOL assessments at a given visit, the QOL scores for dropoffs as well as those of the entire population will be examined for the *previous* visit. Such assessments may indicate that there were earlier reasons why some of the patients did not wish to complete the QOL study.

If no missing data mechanism can be detected, the data will be analyzed assuming missing data are random. Thus, for example, repeated measures analyses will incorporate methodology[16,17] which assumes that there is no missing data mechanism. These repeated measures analyses would also take into account any significant baseline difference in QOL scores between the two arms.

If a missing data mechanism[15] appears to be present, we will employ the following strategies:

- analyze the QOL scores separately for each scheduled visit; and,

- consider imputation procedures which model a missing data mechanism for doing repeated measures analyses.[18,19]

7.4 Sample Size Estimates

Sample size requirements were estimated on the basis of prior information available for the FACT-B. The FACT-B was used for two reasons: first, it is the primary instrument in the study and, second, the NSABP has the best information on breast cancer patients for this instrument. Prior research with the FACT-B indicates that stage I cancer patients have an overall mean of approximately 89.7 $\pm$ 17.6.

Hypotheses 2 and 3 call for paired comparisons of within treatment arm changes across time. If it is assumed that the instrument and the scale scores are normally distributed at the baseline and follow-up time points, and have similar variances, it is possible to estimate the standard deviation of the observed differences using the following equation:

sd (difference)=[(variance time 1+variance time 2) - rho(2covariance)]$^{1/2}$

The maximum sd(difference) occurs when rho (the correlation coefficient of time 1 and time 2 scores) is equal to zero. This is the equivalent of assuming statistical independence between the two distributions and yields a maximum expected sample size. Currently, there are no available data on which to base an estimate of rho in this situation. Given this lack of data, and in order to produce conservative estimates, we have limited our maximum expected rho to 0.30 for the calculation of sample sizes.

It would be useful to be able to detect a true 7-point change in the FACT-B. Given the FACT-B has an expected baseline score of 89.7 $\pm$ 17.6 and a rho=0.30, we would expect a sd(difference)=20.82. The statement of the hypotheses indicates that a one-sided hypothesis test is appropriate. However, due to the fact that we will be testing data from several different QOL scales, the Type I error rate will be set at 0.01 in order to provide an adjustment for multiple comparisons. Based on these paramenters, a total sample size of n=200 subjects equally divided between both arms gives 85% power to detect a true 7 point difference and a total sample size of n=240 subjects equally divided between both arms provides a power of 91%. Since we may expect to lose at least 10-15% of our subjects from the analysis, if we plan for an n=240 subjects, we will end up with approximately n=200-210 subjects for our analysis.

Hypothesis 4 bears most directly on the primary aim of the study. One proposed method to test this hypothesis was to compare indices such as the total number of days with reduced QOL (relative to baseline) and/or a measure of quality-adjusted time on study. Unfortunately, there is nothing in the way of prior quantitative data using such indices on which to base a power analysis for the AC and CMF arms. It is possible, however, to base our power estimates on an analysis using a repeated-measure ANOVA with four measurement points. The hypothesized differences to be tested are expected to occur within the first 30 weeks of the study according to the QOL protocol. Therefore, we can focus on the first 6 months of the study for testing the primary hypothesis. Overlapping examinations appropriate to a repeated measures technique occur at weeks 1 (baseline), 17-18 (AC interim), and 25-30 (six-month).

A number of specific parameters had to be set prior to these calculations:

Type I (α) error - The B-23 instrument is created from the FACT-B, three SF-36 scales, one MOS scale, a symptom checklist, and two linear summary scales. Each one of these components will have to be separately analyzed, raising a multiple comparisons issue for the primary hypothesis test. In order to provide an adjustment for the potential multiple comparisons issue and maintain an experimentwise error rate in the neighborhood of $\alpha = 0.05$, the Type I error rate for the analysis of individual hypothesis tests has been set at $\alpha = 0.01$.

Type II (β) error - A maximum Type II error of 0.20 is acceptable (i.e., 80% power). A Type II error of 0.10 (i.e., 90% power) would be preferable, however.

Missing Data - In most repeated measures techniques, missing data points are usually handled by dropping the subject from the analysis. In effect, missing data points serve to reduce the expected sample size in the power analysis. Two important types of losses are considered in this analysis, patients who quit chemotherapy and patients with substantial examination delays. Current B-23 data suggests that 7-10% of the patients quit their chemotherapy regimen prior to completion. Examination delays due to toxicities or other incidental factors must be expected in this study, even though formal estimates are not currently available. Given this situation we are using a 3-5% "guesstimate" figure for all other data losses. This includes delays due to toxicity that result in examinations occurring outside of the expected weeks, examinations missed due to staff problems and any other occurrences. The power analysis was, therefore, carried out with adjustments to the sample size reflecting missing data of 10% and 15%.

Effect size estimates - The NCSS Power Analysis and Sample Size (PASS) program[20] was used to calculate the repeated measures ANOVA power estimates. The PASS program is based on the techniques outlined by Cohen.[21] In this context, effect size measures are estimated on the basis of an expected f-ratio which is inversely weighted by the expected sample size used in the hypothesis test. For general purposes, effect sizes are classified into small, moderate and large. Given our prior estimates of the basline standard deviation for the FACT-B and a desire to be able to detect a true 7-10 point difference across the first 30 weeks of the trial, we achieve what Cohen and Hintze would classify as a moderate effect size (f =.19-.28). For this analysis, we used an effect size f = 0.25.

Conclusion - With regard to Hypothesis 4, a sample size in the neighborhood of 125 patients per arm is required in order to have sufficient statistical power to detect a true difference of 7-10 points between mean QOL levels in the AC and CMF arms using a repeated measures ANOVA.

8.0 ETHICAL ISSUES

All patients participating in the QOL study will be required to sign a B-23 QOL consent form (Appendix B) prior to baseline assessment. Consent to participate in the QOL study will be obtained separately from the consent to be randomized to the B-23 treatment protocol. Patients who wish to withdraw from the QOL study will be assured that withdrawal will have no effect on their continued participation in B-23. The same principles of confidentiality that apply to personal and clinical data collected in B-23 will be adhered to with respect to QOL data.

9.0 MINORITY ISSUES

There is some evidence in the literature that the perception of quality of life, and the ways in which health problems are expressed, vary from culture to culture. For example, Badia and Alonso found cultural differences between Spanish and American judges when rescaling the Sickness Impact Profile.[22] There are no data concerning potential differences in responses to a cancer-oriented QOL questionnaire between African-Americans and whites in the United States.

The majority of B-23 patients are white, English-speaking women. It is expected that about 3% of those in the QOL study will be French-speaking Quebecers, about 2% will be Hispanic women, and about 9% will be African-American women. With the exception of a few new or modified items that will have to be translated, validated French and Spanish versions of the instruments are available. Because of sample size limitations, we will not be able to compare the effects separately for different cultural or racial groups. Should there be a difference between the two arms of the trial with respect to language, appropriate adjustment will be made in the analysis.

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Version A
Quality of Life Questionnaire
NSABP Protocol B-23

Patient's Name _____

Institution: _____

First 3 Letters of Last Name: ☐☐☐ (1-3)

Study Number: 4 3 ☐☐☐☐☐☐☐ (4-12)

Date Form Completed: ☐☐/☐☐/☐☐ (13-18)
MO DAY YR

Clinic Visit* When Form is Given: ☐ (19)

1=Baseline-Day 1 Course 1 (before chemotherapy)
2=Interim-Week 18 (AC)
3=Interim-Week 30 (completed by CMF mastectomy group only)
4=6 Month Follow-Up (AC)
5=9-Month Follow-up
6=1-Year Follow-Up

*(*Note: The interim assessment does not correspond with a routine follow-up visit and must be mailed to patients.)*

Appendix A contains mock versions of Questionnaires A and B (in English only); they are not for actual patient use. The text for each question will remain the same on the final printed copy booklet provided by the NSABP Biostatistical Center; however, the overall appearance of the form will be slightly different for data entry purposes. Questionnaires (English, French, and Spanish) will be supplied by the NSABP Biostatistical Center, additional copies may be obtained by calling (412) 624-2666, or faxing a written request to (412) 624-1082. **Please only complete questionnaires provided by the NSABP Biostatistical Center and not Xeroxed versions from the protocol document.**

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As of today:

	excellent	very good	good	fair	poor
1. In general, would you say that your health is....	O	O	O	O	O

	much better now	some-what better now	about the same	some-what worse now	much worse now
2. Compared to six months ago, how would you rate your health in general now?	O	O	O	O	O

Please indicate how true each statement has been for you during the past 7 days.

	not at all	a little bit	some-what	quite a bit	very much
3. I have a lack of energy.	O	O	O	O	O
4. I have nausea.	O	O	O	O	O
5. Because of my physical condition, I have trouble meeting the needs of my family.	O	O	O	O	O
6. I have pain.	O	O	O	O	O
7. I am bothered by side effects of treatment.	O	O	O	O	O
8. I feel ill.	O	O	O	O	O

Study Number _____ Date _____

HQ Use (20-27) ☐☐☐☐☐☐☐☐

Please indicate how true each statement has been for you during the past 7 days.

	not at all	a little bit	some-what	quite a bit	very much
9. I am forced to spend time in bed.	O	O	O	O	O
10. I feel distant from my friends.	O	O	O	O	O
11. I get emotional support from my family.	O	O	O	O	O
12. I get support from my friends and neighbors.	O	O	O	O	O
13. My family has accepted my illness.	O	O	O	O	O
14. Family communication about my illness is poor.	O	O	O	O	O
15. I feel close to my partner (or the person who is my main support).	O	O	O	O	O
16. Have you been sexually active during the past year? NO O (1) YES O (2) If yes: I am satisfied with my sex life.	O	O	O	O	O
17. I have confidence in my doctor(s).	O	O	O	O	O
18. My doctor is available to answer my questions.	O	O	O	O	O
19. I feel sad.	O	O	O	O	O
20. I am proud of how I'm coping with my illness.	O	O	O	O	O

Study Number _____ Date _____

HQ Use (28-40) ☐☐☐☐☐☐☐☐☐☐☐☐☐

Please indicate how true each statement has been for you during the past 7 days.

	not at all	a little bit	some-what	quite a bit	very much
21. I am losing hope in the fight against my illness.	O	O	O	O	O
22. I feel nervous.	O	O	O	O	O
23. I worry about dying.	O	O	O	O	O
24. I worry that my condition will get worse.	O	O	O	O	O
25. I am able to work (include work in home).	O	O	O	O	O
26. My work (include work in home) is fulfilling.	O	O	O	O	O
27. I am able to enjoy life.	O	O	O	O	O
28. I have accepted my illness.	O	O	O	O	O
29. I am sleeping well.	O	O	O	O	O
30. I am enjoying the things I usually do for fun.	O	O	O	O	O
31. I am content with the quality of my life right now.	O	O	O	O	O
32. I have been short of breath.	O	O	O	O	O
33. I am self-conscious about the way I dress.	O	O	O	O	O

Study Number _____ Date _____

HQ Use (41-53) ☐☐☐☐☐☐☐☐☐☐☐☐☐

Please indicate how true each statement has been for you during the past 7 days.

	not at all	a little bit	some-what	quite a bit	very much
34. One or both of my arms are swollen or tender.	O	O	O	O	O
35. I feel sexually attractive.	O	O	O	O	O
36. I am bothered by hair loss.	O	O	O	O	O
37. I worry about the risk of cancer in other family members.	O	O	O	O	O
38. I worry about the effect of stress on my illness.	O	O	O	O	O
39. I am bothered by a change in weight.	O	O	O	O	O
40. I am able to feel like a woman.	O	O	O	O	O
41. My health problems limit my everyday physical activities (such as walking or climbing stairs).	O	O	O	O	O

Please indicate how much you have been bothered by each of the following problems during the past 7 days.

	not at all	a little bit	some-what	quite a bit	very much
42. headaches	O	O	O	O	O
43. abdominal pains	O	O	O	O	O

Study Number _____ Date _____

HQ Use (54-63) ☐☐☐☐☐☐☐☐☐☐

Please indicate how much you have been bothered by each of the following problems during the past 7 days.

	not at all	a little bit	some-what	quite a bit	very much
44. vomiting	O	O	O	O	O
45. mouth sores	O	O	O	O	O
46. diarrhea	O	O	O	O	O
47. chest pains	O	O	O	O	O
48. skin problems (including rash, irritation or redness)	O	O	O	O	O
49. dizziness or faintness	O	O	O	O	O
50. pain in the area of my surgery	O	O	O	O	O
51. pain at my intravenous (i.v.) site	O	O	O	O	O
52. numbness or tingling in my hands or feet	O	O	O	O	O
53. fever or shivering (shaking, chills)	O	O	O	O	O
54. bladder problems	O	O	O	O	O
55. constipation	O	O	O	O	O
56. hot flashes	O	O	O	O	O

Study Number _____ Date _____

HQ Use (64-76) ☐☐☐☐☐☐☐☐☐☐☐☐☐

Please indicate how much you have been bothered by each of the following problems during the past 7 days.

	not at all	a little bit	some-what	quite a bit	very much
57. genital itching or irritation	O	O	O	O	O
58. mood swings	O	O	O	O	O

Please indicate the answer that comes closest to the way you have been feeling during the past 7 days.

	none of the time	a little of the time	some of the time	a good bit of the time	most of the time	all of the time
59. Did you feel full of pep?	O	O	O	O	O	O
60. Did you have a lot of energy?	O	O	O	O	O	O
61. Did you feel worn out?	O	O	O	O	O	O
62. Did you feel tired?	O	O	O	O	O	O

Study Number _____ **Date** _____

HQ Use (77-82) ☐☐☐☐☐☐

63. As of today, to what extent have you resumed all of your normal activities (both inside and outside the home and at work, if employed)?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
O	O	O	O	O	O	O	O	O	O	O

64. As of today, how would you rate your <u>overall quality of life</u> on an 11-point scale between death and perfect health?

	0	1	2	3	4	5	6	7	8	9	10	
death	O	O	O	O	O	O	O	O	O	O	O	perfect health

THANK YOU FOR TAKING TIME TO COMPLETE THIS QUESTIONNAIRE

Study Number _____ Date _____

HQ Use (83-85) ☐☐☐ (86-87) ☐☐

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Version B
Quality of Life Questionnaire
NSABP Protocol B-23

Patient's Name: _____

Institution: _____

First 3 Letters of Last Name: ☐☐☐ (1-3)

Study Number: 4 3 ☐☐☐☐☐☐☐ (4-12)

Date Form Completed: ☐☐/☐☐/☐☐ (13-18)
MO DAY YR

Clinic Visit When Form is Given: ☐ (19)

2=Course 2
3=Course 3
4=Course 4
5=Course 5 (CMF)
6=Course 6 (CMF)

Appendix A contains mock versions of Questionnaires A and B (in English only); they are not for actual patient use. The text for each question will remain the same on the final printed copy booklet provided by the NSABP Biostatistical Center; however, the overall appearance of the form will be slightly different for data entry purposes. Questionnaires (English, French, and Spanish) will be supplied by the NSABP Biostatistical Center, additional copies may be obtained by calling (412) 624-2666, or faxing a written request to (412) 624-1082. **Please only complete questionnaires provided by the NSABP Biostatistical Center and not Xeroxed versions from the protocol document.**

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As of today:

	excellent	very good	good	fair	poor
1. In general, would you say that your health is....	O	O	O	O	O

Please indicate how true each statement has been for you since the beginning of your last treatment cycle.

	not at all	a little bit	some-what	quite a bit	very much
2. I have a lack of energy.	O	O	O	O	O
3. I have nausea.	O	O	O	O	O
4. Because of my physical condition, I have trouble meeting the needs of my family.	O	O	O	O	O
5. I have pain.	O	O	O	O	O
6. I am bothered by side effects of treatment.	O	O	O	O	O
7. I feel ill.	O	O	O	O	O
8. I am forced to spend time in bed.	O	O	O	O	O
9. I feel distant from my friends.	O	O	O	O	O
10. I get emotional support from my family.	O	O	O	O	O
11. I get support from my friends and neighbors.	O	O	O	O	O
12. My family has accepted my illness.	O	O	O	O	O

Study Number _____ Date _____

HQ Use (20-31) ☐☐☐☐☐☐☐☐☐☐☐☐

Please indicate how true each statement has been for you since the beginning of your last treatment cycle.

	not at all	a little bit	some-what	quite a bit	very much
13. Family communication about my illness is poor.	○	○	○	○	○
14. I feel close to my partner (or the person who is my main support).	○	○	○	○	○
15. Have you been sexually active during the past year? NO ○ (1) YES ○ (2) If yes: I am satisfied with my sex life.	○	○	○	○	○
16. I have confidence in my doctor(s).	○	○	○	○	○
17. My doctor is available to answer my questions.	○	○	○	○	○
18. I feel sad.	○	○	○	○	○
19. I am proud of how I'm coping with my illness.	○	○	○	○	○
20. I am losing hope in the fight against my illness.	○	○	○	○	○
21. I feel nervous.	○	○	○	○	○
22. I worry about dying.	○	○	○	○	○
23. I worry that my condition will get worse.	○	○	○	○	○
24. I am able to work (include work in home).	○	○	○	○	○

Study Number _____ Date _____

HQ Use (32-44) ☐☐☐☐☐☐☐☐☐☐☐☐☐

Please indicate how true each statement has been for you since the beginning of your last treatment cycle.

	not at all	a little bit	some-what	quite a bit	very much
25. My work (include work in home) is fulfilling.	O	O	O	O	O
26. I am able to enjoy life.	O	O	O	O	O
27. I have accepted my illness.	O	O	O	O	O
28. I am sleeping well.	O	O	O	O	O
29. I am enjoying the things I usually do for fun.	O	O	O	O	O
30. I am content with the quality of my life right now.	O	O	O	O	O
31. I have been short of breath.	O	O	O	O	O
32. I am self-conscious about the way I dress.	O	O	O	O	O
33. One or both of my arms are swollen or tender.	O	O	O	O	O
34. I feel sexually attractive.	O	O	O	O	O
35. I am bothered by hair loss.	O	O	O	O	O
36. I worry about the risk of cancer in other family members.	O	O	O	O	O
37. I worry about the effect of stress on my illness.	O	O	O	O	O

Study Number _____ Date _____

HQ Use (45-57) ☐☐☐☐☐☐☐☐☐☐☐☐☐

Please indicate how true each statement has been for you since the beginning of your last treatment cycle.

	not at all	a little bit	some-what	quite a bit	very much
38. I am bothered by a change in weight.	O	O	O	O	O
39. I am able to feel like a woman.	O	O	O	O	O
40. My health problems limit my everyday physical activities (such as walking or climbing stairs).	O	O	O	O	O

Please indicate how much you have been bothered by each of the following problems since the beginning of your last treatment cycle.

	not at all	a little bit	some-what	quite a bit	very much
41. headaches	O	O	O	O	O
42. abdominal pains	O	O	O	O	O
43. vomiting	O	O	O	O	O
44. mouth sores	O	O	O	O	O
45. diarrhea	O	O	O	O	O

Study Number _____ Date _____

HQ Use (58-65) ☐☐☐☐☐☐☐☐

Please indicate how much you have been bothered by each of the following problems since the beginning of your last treatment cycle.

	not at all	a little bit	some-what	quite a bit	very much
46. chest pains	O	O	O	O	O
47. skin problems (including rash, irritation or redness)	O	O	O	O	O
48. dizziness or faintness	O	O	O	O	O
49. pain in the area of my surgery	O	O	O	O	O
50. pain at my intravenous (i.v.) site	O	O	O	O	O
51. numbness or tingling in my hands or feet	O	O	O	O	O
52. fever or shivering (shaking, chills)	O	O	O	O	O
53. bladder problems	O	O	O	O	O
54. constipation	O	O	O	O	O
55. hot flashes	O	O	O	O	O
56. genital itching or irritation	O	O	O	O	O
57. mood swings	O	O	O	O	O

Study Number _____ Date _____

HQ Use (66-77) ☐☐☐☐☐☐☐☐☐☐☐☐

Please indicate the answer that comes closest to the way you have been feeling since the beginning of your last treatment cycle.

	none of the time	a little of the time	some of the time	a good bit of the time	most of the time	all of the time
58. Did you feel full of pep?	O	O	O	O	O	O
59. Did you have a lot of energy?	O	O	O	O	O	O
60. Did you feel worn out?	O	O	O	O	O	O
61. Did you feel tired?	O	O	O	O	O	O

62. As of today, to what extent have you resumed all of your normal activities (both inside and outside the home and at work, if employed)?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
O	O	O	O	O	O	O	O	O	O	O

63. Please score your overall quality of life since the beginning of your last treatment cycle on an 11-point scale between death and perfect health?

	0	1	2	3	4	5	6	7	8	9	10	
death	O	O	O	O	O	O	O	O	O	O	O	perfect health

Study Number _____ **Date** _____

HQ Use (78-81) ☐☐☐☐ (82-84) ☐☐☐ (85-86) ☐☐

THANK YOU FOR TAKING TIME TO COMPLETE THIS QUESTIONNAIRE

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Version as of 4/16/97

MODEL CONSENT
CONSENT TO ACT AS A SUBJECT IN AN RESEARCH STUDY

TITLE: **National Surgical Adjuvant Breast and Bowel Project (NSABP) Quality of Life Study**

INVESTIGATOR(S): **[Supply specific information for your institution]**

DESCRIPTION: You are being invited to take part in this study because you have agreed to participate in NSABP Protocol B-23, which is comparing two chemotherapy regimens, Adriamycin-cyclophosphamide (AC) and cyclophosphamide-methotrexate-5-FU (CMF), and is also studying the worth of the hormonal drug tamoxifen, in women with breast cancers similar to yours.

The main purpose of this quality-of-life study is to measure how the quality of women's lives (their physical and emotional well-being) is affected by two different chemotherapy regimens. In addition, this study may provide some information on how the other treatments in this study (mastectomy, lumpectomy with radiation therapy, and tamoxifen) affect a patient's quality of life.

If you agree to participate, you will be asked to fill out a 15- to 20-minute questionnaire at the following times over the next year:

1) Before you begin your chemotherapy treatments,
2) At the beginning of each chemotherapy treatment cycle,
3) Approximately 6 weeks after your chemotherapy has ended,
4) At two or three other follow-up visits within your first year on the B-23 study.

You can fill out the questionnaire form before your treatment begins on the first day of each cycle of your treatment. A member of the research staff will be available if you need any help or have any questions. After chemotherapy, you will complete the questionnaire when you see your physician for follow-up. One questionnaire will also be sent to you by mail, and you can return it by mail.

Study Number_____ Patient Initials_____

RISKS AND BENEFITS: There are no physical risks from participating in this study. You may find some questions emotionally difficult to answer; however, you can skip any questions that you do not want to answer.

The NSABP researchers believe that this quality-of-life information will assist other researchers, health care providers, and future patients in weighing the risks and benefits of these treatment options. If the B-23 study shows that both chemotherapy regimens produce similar results, then information about their impact on quality of life will be especially important.

ALTERNATIVE TREATMENTS: Not applicable

COSTS AND PAYMENTS: There will be no additional cost to you for participating in the study. You will not receive any payment for being in the study.

NEW INFORMATION: Any new information developed during the course of this research that may relate to your willingness to participate will be provided to you.

CONFIDENTIALITY: Any information about you obtained from this research will be kept confidential, and you will never be identified in any report. In order to evaluate your overall health, your personal physician(s) will be asked to provide information concerning your medical care to the group conducting this research study. Your study records, just like hospital records, may be requested by court order. When results of a study such as this are reported in medical journals or at meetings, the names of participants remain confidential. Authorized representatives of the National Cancer Institute (NCI), the Food and Drug Administration (FDA), the NSABP, and the appropriate pharmaceutical companies may examine and copy your medical record relating to this research, but all information examined will be kept confidential.

RIGHT TO WITHDRAW: You are free to refuse to participate in this study or to withdraw at any time for any reason. Your decision to do so will not adversely affect your care at this institution or cause a loss of benefits to which you might otherwise be entitled. **If you decline to participate in this quality-of-life study, it will not affect your ability to participate in the B-23 treatment study.**

COMPENSATION FOR ILLNESS OR INJURY: In the unlikely event of an injury or illness resulting from your participation in this quality-of-life study, you will receive whatever immediate emergency treatment is required at your expense. You will not be paid any money for pain and suffering.

****

Study Number_____ Patient Initials_____

VOLUNTARY CONSENT: I certify that I have read this consent form, or that it has been read to me. Any questions I had, including an explanation of all terminology, have been answered to my satisfaction. I also understand that any future questions I may have pertaining to the research will be answered by Dr(s)_____ at _____. Any questions I have concerning my rights as a research subject will be answered by the following:

Office/Person:
Address:
Phone:

A copy of this consent form will be given to me.

My signature below means that I have freely agreed to participate in this research study.

_____ _____
Date Patient's Signature

_____ _____
Date Witness's Signature

I certify that the nature and purpose, the potential benefits, and potential risks associated with participation in this research study, have been explained to the above individual and that any questions about this information have been answered.

_____ _____
Date Investigator's Signature

Study Number_____ Patient Initials_____

APPENDIX

g. B-30 HRQL-related sections of Protocol

NSABP PROTOCOL NO. B-30

A THREE-ARM RANDOMIZED TRIAL TO COMPARE ADJUVANT ADRIAMYCIN AND CYCLOPHOSPHAMIDE FOLLOWED BY TAXOTERE (AC→T); ADRIAMYCIN AND TAXOTERE (AT); AND ADRIAMYCIN, TAXOTERE, AND CYCLOPHOSPHAMIDE (ATC) IN BREAST CANCER PATIENTS WITH POSITIVE AXILLARY LYMPH NODES

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Protocol Chair:	Sandra Swain, M.D.
Protocol Officer:	Roy Smith, M.D.
Protocol Statistician:	James Dignam, Ph.D.

STUDY DRUGS:

Docetaxel (Taxotere)	NSC#628503	Supplied by Rhône-Poulenc Rorer via the NCI
Doxorubicin (Adriamycin)	NSC#123127	Commercial
Cyclophosphamide	NSC#26271	Commercial
Tamoxifen	NSC#180973	Commercial

Version as of August 12, 1998 (Please destroy all other versions)

such as cyclophosphamide are often the cause of ovarian dysfunction.[40] This study will compare the incidence of amenorrhea in each treatment arm and assess the association of amenorrhea with symptoms and QOL. (Since the AC arm does not include cyclophosphamide, there may be less ovarian dysfunction with this regimen.) At the same time, drug-induced amenorrhea may be a favorable prognostic factor in breast cancer,[41] although this effect remains controversial. Documenting menstrual history in women participating in this protocol may provide a unique opportunity to assess the effect of induced menopause on DFS and S.

9.3 Quality of life measures

The following measures will be used to assess QOL:

- Functional Assessment of Cancer Therapy - Breast (FACT-B)
- Treatment-Specific Symptom Checklist
- Vitality Scale (SF-36)
- Quality of Life Rating Scale

The FACT-B questionnaire is a multidimensional, 44-item, cancer-oriented measure of QOL developed by Cella et al.[42] Five subscales provide scores for physical well-being, social/family well-being, patient/physician relationship, emotional well-being, and functional well-being. Nine additional questions refer to problems commonly experienced by women with breast cancer. The FACT questionnaire has been extensively validated and completed by thousands of cancer patients over the past several years, including two NSABP protocols, B-23 and C-06. The symptom checklist will assess the frequency and severity of symptoms potentially associated with each treatment regimen. As in previous NSABP QOL studies, the list of symptoms includes common side effects of chemotherapy as well as symptoms specific to the agents used in the current protocol. The four-item Vitality Scale is part of the MOS SF-36 instrument.[43] The scale is useful in detecting common but less specific side effects of cancer therapy, such as fatigue and lack of energy. The QOL rating scale will evaluate the patient's overall perception of QOL on a scale from 0 to 10. This will facilitate the calculation of quality-adjusted S for the chemotherapy treatment groups.

9.4 Menstrual history assessment

Menstrual history will be documented with a standard set of questions (Menopause and Menstrual History Questionnaire, MMHQ). These questions have been used in previous studies of women receiving chemotherapy.[44] Two versions will be employed: a baseline version and a follow-up version. The MMHQ includes questions about the use of hormonal replacement therapy and

hormonal contraceptives, hysterectomy, oophorectomy, and any changes in menstruation before, during, and after chemotherapy.

At baseline, the MMHQ will be administered to all women as part of the QOL questionnaire. During the follow-up, only women who were premenopausal (or perimenopausal) at baseline will be asked questions about menstrual history. Postmenopausal women will receive the QOL questionnaire without the MMHQ section.

In women who have not had a hysterectomy, menopause will be defined as complete cessation of menstrual periods for 12 months or more. Women who have had a hysterectomy without an oophorectomy will be considered postmenopausal if they are 55 years of age or older.

9.5 Assessment schedule

The QOL questionnaire will be administered at the following time points:

- at baseline
- on day 1 of cycle 4 of chemotherapy (week 9)
- at 6 months
- at 12 months
- at 18 months
- at 2 years

The baseline questionnaire should be administered after the consent is signed, but prior to randomization. If a patient is taken off protocol therapy before cycle 4, QOL should be evaluated as scheduled at week 9, by mail or telephone. For telephone administration, the questionnaire should be mailed to the patient in advance. The 6-month assessment in the AC→T arm may have to be postponed in case of delays in therapy. In these patients, the questionnaire should be administered 3 weeks after the last dose of Taxotere or at 6 months, whichever is later. In women who are taken off protocol therapy, as well as those who experience breast cancer recurrence or a second primary cancer, follow-up evaluations of QOL should be carried out according to schedule.

17.0 STATISTICAL CONSIDERATIONS

17.1 Main trial

17.1.1 *Randomization and accrual*

Assignment of treatment to patients will be balanced with respect to number of positive nodes (1-3, 4-9, 10+), tamoxifen assignment (yes, no), type of surgery (mastectomy, lumpectomy) and radiation received, and institution, using a biased-coin minimization algorithm.[46]

Based on accrual rates to recent trials involving node-positive patients (NSABP B-25 and B-28), we anticipate monthly accrual of 115 patients.

17.1.2 *Endpoints and primary statistical analyses*

The primary endpoint for the study will be survival time (S), defined as time from study entry to death from any cause. In addition, disease-free survival (DFS), defined as time to recurrence at any local, regional, or distant anatomic site, occurrence of contralateral breast cancer or any other second primary cancer, or death from any cause prior to these events, will be compared among treatment groups.

Distributions of S and DFS will be computed using the method of Kaplan and Meier, and compared by stratified log-rank tests.[47,48] Treatment comparisons will also be made using the Cox proportional hazards model to control for the potential confounding influence of other prognostic variables.[49]

17.1.3 *Failure rates*

We denote the concurrent administration of AC and Taxotere as ATC and the sequential administration as AC→T. From previous studies, we have observed an annual death rate of 0.045 for patients receiving AC. As we anticipate a greater proportion of patients with a large number of positive nodes, for the planning of this trial we will assume an annual failure rate of 0.05. With the addition of Taxotere, we assume a 25% reduction in the rate, or an annual failure rate of (0.05).75 = 0.0375. Specifically, we assume this rate for the least efficacious of the three-drug regimens containing Taxotere (i.e., ATC or AC→T).

17.1.4 *Primary hypotheses and sample size requirements*

Two primary statistical hypotheses will be evaluated in this study:

- whether either the concurrent addition or sequential addition of Taxotere to AC is superior, and
- whether the two-drug combination A plus Taxotere (AT) is at least as efficacious as the three-drug regimens.

In order to evaluate whether concurrent or sequential addition of Taxotere to AC is superior, we assume that an additional 25% reduction in mortality rate for either the concurrent (ATC) or sequential (AC→T) addition of Taxotere to the AC regimen would constitute a clinically significant advantage over the less efficacious administration of the three agents. We require that the comparison have power of at least 0.80 to detect a difference of this magnitude or greater, at a two-sided α level of 0.05.

Concurrently with this goal, we wish to test whether AT is equivalent to each of the regimens containing cyclophosphamide. Consider, for example, the comparison of AT with ATC. Formally, we will test the hypothesis that the mortality rates are equal

$$H_0: \lambda_{ATC} = \lambda_{AT}$$

against the alternative hypothesis that the ATC regimen has a 2% lower mortality rate than does AT

$$H_A: \lambda_{ATC} = 0.8 \bullet \lambda_{AT}$$

If H_0 is rejected in favor of H_A, we will conclude that ATC is superior to AT. Otherwise, we will consider the regimens to be equivalent. The test will be carried out at a one-sided level of significance where $\alpha = 0.15$ and Type II error rate $\beta=0.10$ (power = 0.90). Thus, if the two regimens are truly equivalent (equal mortality rates), there is a 0.15 probability of erroneously concluding that ATC is superior. On the other hand, if ATC decreases the mortality rate by 20%, there is a 0.10 probability of erroneously concluding equivalence. If the true relative risk is $\lambda_{ATC}/\lambda_{AT}=0.905$, so that the addition of cyclophosphamide decreases the mortality rate by 9.5%, there is roughly a 50-50 chance of concluding the regimens are equivalent. The test for equivalency of AT with AC→T is analogous to the above.

To jointly satisfy the goals of establishing whether ATC or AC→T is superior *and* whether AT is as efficacious as the regimens containing

cyclophosphamide, we require that a minimum of 432 events be accumulated between each pair of treatment groups (ATC *vs* AC→T, AT *vs* ATC, AT *vs* AC→T) before definitive hypothesis tests are performed. Taking into account the assumed accrual of 115 patients per month and the anticipated failure rates given above, a total of 3680 patients accrued over 32 months and followed for an additional 52 months would provide the requisite events for the definitive analysis, resulting in a total study duration of approximately 7 years.

17.1.5 *Interim and final analysis*

Three interim analyses and one definitive analysis of the total events (deaths) will be scheduled at equal intervals. Under a null hypothesis of equal outcomes for the three treatments, there will have occurred 648 deaths at the time of definitive analysis. Interim analyses will be performed as follows:

- Interim analysis 1 will be performed when either 162 deaths have occurred among all treatment arms or 71 deaths have occurred among patients on the least favorable treatment arm.

- Interim analysis 2 will be performed when either 324 deaths have occurred among all treatment arms or 131 deaths have occurred among patients on the least favorable treatment arm.

- Interim analysis 3 will be performed when either 486 deaths have occurred among all treatment arms or 190 deaths have occurred among patients on the least favorable treatment arm.

- The definitive analysis will be performed when either 648 deaths have occurred among all treatment arms or 237 deaths have occurred among patients on the least favorable treatment arm.

The event totals for the interim analyses are chosen to represent equal increments of total event information required for definitive analysis. The maximum number of events for the least favorable treatment arm is chosen such that if an imbalance develops which is likely to lead to the rejection of one of the primary statistical hypotheses, then an interim analysis will be triggered. These analyses are anticipated to occur approximately at 2.75, 4.25, 5.75, and 7.0 years from the inception of randomization.

At each interim analysis, two statistical hypotheses will be tested, using separate early stopping significance criteria in keeping with the goals of the study: an efficacy comparison between the two three-drug regimens and an equivalence comparison between AT and the three-drug regimens.

For purposes of monitoring, we will restrict this comparison to the superior of the three-drug regimens and the AT group (since only the more extreme comparison is relevant for early stopping). Bounds for early stopping were obtained using the method of Fleming, Harrington, and O'Brien.[50] The parameter μ, which determines unconditional early stopping probabilities under H_0, was fixed at 0.10 for both the efficacy and equivalence comparisons.

For the comparison of the two three-drug regimens, the standardized z-values associated with the log-rank statistics for the interim and final analyses are {|3.143|, |3.100|, |3.045|, |1.974|}, corresponding to two-sided alpha levels {0.0017, 0.0019, 0.0023, 0.0483}. For the comparison of the superior of the two three-drug regimens to AT, the z-values associated with the log-rank statistics for the three interim analyses are {2.58, 2.46, 2.37}, corresponding to one-sided alpha levels {0.005, 0.007, 0.009}. The definitive analysis will involve comparisons of each three-drug regimen to AT, and if in either comparison the z-value associated with the standardized log-rank statistic exceeds 1.07 ($\alpha = 0.14$), then we will conclude that AT is inferior to that three-drug regimen.

17.1.6 *Monitoring of adverse events and data quality*

The occurrence of adverse events, including toxicities, second primary cancers, and deaths (on therapy or prior to evidence of disease progression), will be monitored continuously. Guidelines for reporting adverse events to all appropriate parties are detailed in Section 12.0. In addition, summaries of adverse events and toxicities will be prepared and reviewed at monthly meetings of the NSABP Toxicity Committee.

Throughout the accrual and active treatment periods of the trial, progress reports will be prepared and presented to the NSABP Data Monitoring Committee (DMC) at 6-month intervals. These reports will include an assessment of toxicities, second primary cancers and on-therapy deaths, a comparison of actual and projected accrual, and an assessment of data quality, including data delinquency and rates of eligibility. After accrual is closed, adverse events and other information will be presented to the DMC, together with interim analysis results.

17.2 Quality of life (QOL) study

17.2.1 *Background*

There are two components to the B-30 QOL study: first, the QOL Questionnaire (QLQ) which includes the FACT-B, Symptom Checklist (SCL) and SF-36 vitality scale; and second, the baseline and follow-up

versions of the Menopause and Menstrual History Questionnaire (MMHQ). According to the rationale in Section 9.1, the QLQ tests the primary hypotheses regarding effects of the order and number of drugs in each treatment arm on the QOL of the patients. The MMHQ focuses on the secondary aim of assessing the frequency of amenorrhea in each treatment arm and how it relates to symptoms, QOL, and DFS. Both questionnaires will be administered at baseline, day 1 of cycle 4, 6 months, 12 months, 18 months, and 24 months.

17.2.2 *Sample size and power estimates for the QLQ*

Of the component instruments in the QLQ, the FACT-G is the best known in terms of cancer patients. Since the patients enrolled in B-30 will have positive nodes, we anticipate somewhat lower mean scores for the FACT-G (75-80, with a standard deviation of 15-20), than those projected for the QOL component of NSABP B-23, which enrolled only node-negative patients. Since we are primarily interested in comparisons between arms, as opposed to comparisons within arms, a 7-10 point difference between the arms will be considered a clinically significant finding for the primary aim of the study. Given this background and using a simple comparison of means, a conservative estimate indicates that it would take about 150 patients in each arm to have an 87% chance of detecting a 7-point difference at a 0.01 level of significance. Drop-out rates may be as high as 30-33% in B-30. Therefore, in order to have 150 patients in each arm completing therapy, it will be necessary to enroll approximately 225 subjects in each arm. (Patients who quit therapy will still be asked to complete the QLQ form at routine follow-up visits.) This simple model suggests that we would need approximately 675 subjects evenly divided among the three arms to test the primary QOL hypotheses. It would also be preferable if we could stratify samples within each arm according to a binary age variable ($\leq$49, $\geq$50 years). This would require a doubling of the sample size in each arm to 450 patients or a total of 1350 patients evenly divided among the three arms. Experience from B-28 suggests that recruitment to these two age groups is approximately equal and, therefore, would minimize the problem of uneven recruitment to different age groups. Furthermore, the final statistical analysis would probably be carried out using a repeated measures ANOVA model. Under these circumstances, we may expect that the power estimates provided here are relatively conservative.

17.2.3 *Sample size for the menstrual history assessment*

The baseline version of the MMHQ will be given to all study participants prior to randomization. The follow-up version of the MMHQ will be given only to women who are pre- and perimenopausal at baseline. (See

Section 9.4 for definitions related to menopausal status.) Given the specific aims of the menstrual history assessment study, it will be necessary to give this instrument through month 24 to all patients who are pre- or perimenopausal at baseline (approximately 1800 women). Reasons for this include the stated intention of trying to detect an association between induced menopause and DFS and the fact that we have no way of estimating the differences in the proportions of women experiencing amenorrhea in the separate treatment arms.

APPENDIX

h. C-06 HRQL-related sections of Protocol
(English, French and Spanish Instruments at Rear)

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NSABP PROTOCOL C-06

A CLINICAL TRIAL COMPARING ORAL URACIL/FTORAFUR (UFT) PLUS LEUCOVORIN (LV) WITH 5-FLUOROURACIL (5-FU) PLUS LV IN THE TREATMENT OF PATIENTS WITH STAGES II AND III CARCINOMA OF THE COLON

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STUDY DRUGS:

Uracil/Ftorafur	Supplied by Bristol-Myers Squibb Pharmaceutical Research Institute
Leucovorin (oral)	Supplied by Bristol-Myers Squibb Pharmaceutical Research Institute
Leucovorin (i.v.)	Commercially Available
5-Fluorouracil	Commercially Available

Draft Version as of December 27, 1996 (PLEASE DESTROY ALL OTHER VERSIONS)

8.0 QUALITY-OF-LIFE (QOL) ASSESSMENT

Two instrument packets will be used to assess patients' QOL on the C-06 study. The following measures have been incorporated into Questionnaire A:

- Symptom Distress Scale
- Treatment-Specific Symptom Checklist
- Eastern Cooperative Oncology Group (ECOG) Burden of Care (partial)

The following measures have been incorporated into Questionnaire B:

- Functional Assessment of Cancer Therapy, Colon Version 3 (FACT-C)
- Vitality Scale (MOS SF-36)
- Two additional QOL questions:
  (1) Utility rating scale, and
  (2) Return to normal activity

The Symptom Distress Scale contains 11 items that assess general symptoms associated with chemotherapy.[85] The Treatment-Specific Symptom Checklist contains 6 items developed for Southwest Oncology Group (SWOG) colorectal cancer studies, and additional questions specific for C-06. Three questions were taken from the ECOG Burden of Care Form. This form assesses the burden associated with i.v. administration of chemotherapy, repeated clinic visits, and overall QOL.

The FACT questionnaire is a multidimensional, 44-item, cancer-oriented measure of QOL developed by David Cella.[86] Five subscales provide scores for physical well-being, social/family well-being, relationship with physician, emotional well-being, and functional well-being. Nine additional questions refer to problems commonly experienced by patients with colorectal cancer. Although this scale is relatively new, it has been extensively validated and is rapidly gaining acceptance among QOL researchers. The four-item Vitality Scale is part of the MOS SF-36.[87] The scale is useful in detecting common, but less-specific, side effects of cancer therapy, such as fatigue and lack of energy. The QOL rating scale will evaluate the patient's overall perception of QOL on a scale from 0 to 10. The assessment will provide a single QOL coefficient (0-1) for the purpose of "utility" estimation. This will facilitate the calculation of quality-adjusted survival for the two chemotherapy treatment groups. The extent to which the patient is able to resume normal activities is not adequately ascertained by the above instruments. This issue will be addressed by a question developed by David Cella.*

---

*Cella DF, personal communication, 1995.

8.1 Schedule for the Assessment of QOL

As described in Section 8.0, two QOL questionnaires will be used for C-06. Questionnaire A will be administered at the following time points:

- At baseline (after the consent is signed, but before randomization)
- On day 1 of each cycle of chemotherapy (with the exception of cycle 1, since the baseline assessment is done before randomization)
- At one year

This will result in four assessments for the 5-FU + LV regimen and six assessments for the UFT + LV regimen. This approach was designed to capture, longitudinally, the difference in symptoms and treatment burden between the two regimens.

Questionnaire B will be administered at three of the same times that Questionnaire A is given:

- At baseline (after the consent is signed, but before randomization)
- Two-thirds of the way through chemotherapy:
  - On day 1, cycle 3, for the 5-FU + LV regimen: (week 16)
  - On day 1, cycle 4, for the UFT + LV regimen: (week 15)
- At one year

This will provide a more detailed comparison of the on-therapy QOL of patients accrued to the C-06 study.

factors in one [redacted] to see if [redacted] is a sub[redacted] of patients f[redacted]om the t[redacted]nt behave[redacted]erently from w[redacted] as observed [redacted] overall trial.

18.1.8.2 ~~Time To Treatment Failure~~ Disease Free Survival

We will perform the same analyses using time to treatment failure as the endpoint, as we will have done using survival as an endpoint.

18.1.8.3 Toxicity

In addition to presenting toxicities in a descriptive manner, we will formally compare the proportion of patients experiencing life-threatening toxicities, excluding hematologic toxicities and severe or greater toxicities. The results of these analyses will be of particular interest if the two regimens are similar in terms of survival benefit. These data, as well as delinquency data, will be reviewed by the NSABP Data Monitoring Committee (DMC) at semiannual meetings.

18.1.8.4 Review of Protocol Assumptions and Accrual Rate

The NSABP DMC will be notified of the observed death rate on the 5-FU + LV regimen at the end of the second year of accrual. If this annual death rate is less than 6% per year, the NSABP will ask the committee to consider a recommendation to increase the sample size or extend the follow-up period. If the monthly accrual rate is less than 75% of the projected rate after the study has been open for a year, the DMC will determine whether a change to the protocol is required.

18.2 Quality-of-Life (QOL) Substudy

18.2.1 Background

QOL findings represent one among a hierarchy of outcome factors used in this study. Other factors include disease-free survival (DFS), survival (S), levels and kinds of treatment-associated toxicities, and ease of treatment administration. Although the QOL findings are uniquely designed to reflect the perspective of the patient, they will have to be balanced against the other clinical factors in making overall recommendations based on this trial.

This section will focus specifically on the analysis of the QOL data and the central question of whether it is possible to identify statistically and clinically significant QOL differences between the two arms of the trial. We are particularly interested in the question of whether UFT+LV, when compared to 5-FU+LV, has a smaller adverse effect on overall QOL during the course of treatment.

The QOL component of this trial uses two different questionnaires (A and B), which have been developed from existing instruments and the clinical experience of the investigators. Each questionnaire will be administered on a different schedule and is focused on different issues. The description of the analysis of the data from each questionnaire will be handled separately, starting with Questionnaire B then moving to Questionnaire A.

18.2.2 Stratification

Analyses will be stratified by age (<59 and ≥ 60 years), sex, and ethnicity (white and nonwhite).

18.2.3 Questionnaire B (QB)

QB is composed of the FACT-C (items 1-37), the SF-36 Vitality Scale (items 38-41) and two summary QOL items, using a linear visual scale (items 42-43). It will be administered on three occasions (see Section 8.1): at baseline, at the 15-16 week of treatment, and at 1 year following the initiation of treatment. This questionnaire is intended to provide broad summary estimates of the patients' QOL and overall functioning at key time points in the trial.

The first analytic issue using QB is the comparison of baseline QOL scores. We expect (null hypothesis) that the patients in the two trial arms will have statistically equivalent baseline QOL scores since the instrument will have been administered before the random assignment of treatment. A nonparametric test for independent samples (Wilcoxon rank-sum/Mann-Whitney)[90] will be used to test this hypothesis. The large size of the unstratified sample used in the trial (n=1452) could lead to the identification of statistically significant but clinically unimportant differences between the two trial arms. For this reason, it will be necessary to develop some prior criteria for what will be considered clinically important differences on specific instruments. In the case of the FACT-C scale, for example, a difference of less than three points would not be considered important on common sense clinical grounds even if a statistical level of significance ($p \leq 0.05$) is

achieved.* Due to reduced sample sizes, this is not as much of a problem when stratified analyses are carried out.

The second analytic issue is whether there are statistically significant effects for time and group over the 12-month period of observation. Initially, longitudinal plots will be used (mean, median, and 95% CI) to descriptively compare the patterns of QOL scores in the two treatment arms across the three study time points. Hypothesis testing will be carried out using repeated measures analysis of variance procedures for continuous and categorical data.[91-94] Linear contrasts and adjusted post-hoc comparisons will be used to compare the 15-16 week and 1-year time points to the baseline QOL scores. In this analysis, we expect to observe a main effect for time, that is, a statistically significant decline in overall QOL indices for both trial arms at the 15-16 week time point. In addition, we want to test the possibility that this overall decline at the 15-16 week time point is significantly less adverse for the UFT+LV arm than for the 5-FU+LV arm, i.e., a statistically significant [time x arm] interaction term. If the latter effect is observed, an independent assessment will be made to determine whether this represents a meaningful clinical difference in overall QOL scores. Finally, if clinically and statistically significant differences are observed between the UFT+LV and the 5-FU+LV arms of the trial on the FACT-C, a secondary analysis will be carried out to investigate whether this difference is due to changes in specific subscales (e.g., physical well-being, social/family well-being, emotional well-being, colon cancer specific concerns) or represents a general decline in overall QOL. Nonparametric equivalents to an ANOVA[95] and t-test (Wilcoxon/Mann Whitney)[90] will be used to initially evaluate such data.

18.2.4 Questionnaire A (QA)

QA is composed of the 11-item Symptom Distress Scale (SDS; items 1-11),[85] a supplementary symptom checklist (items 12-28) and three items from the ECOG Burden of Care Scale (BCS; items 29-31). This questionnaire will be given at baseline, on the first day of each treatment cycle (except cycle 1) and at 1 year (see Section 8.1). This means that QB will be administered to patients in the 5-FU + LV arm on four occasions and to those in the UFT + LV arm on six occasions.

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*Cella DF, personal communication, 1995.

The QA was designed to focus on the side effects of treatment and to provide greater insight into specific toxicities and coping problems that affect the patients in both arms of the trial. The psychometric properties of the 11-item SDS have been extensively studied, and an additive score can be used to characterize patient responses. The other components of QA have a face validity but have not been subjected to extensive psychometric testing. For this reason, the symptom checklist and burden of care items will have to be analyzed on an individual basis.

Due to the nature of the instrument and the schedule of administration, the analyses carried out on QA tend to be more exploratory in nature than for QB. Initially, baseline SDS scores will be compared using nonparametric tests (Wilcoxon/Mann-Whitney)[90] to determine whether the patients in both treatment arms are at statistically equivalent levels of symptom distress. The primary problem in analyzing the post-baseline data arises from the fact that a different number of assessments are being carried out in each arm and that these assessments are generally not administered at comparable time points. In this situation, longitudinal plots using means, medians, and confidence intervals are an important method of analysis. If statistically significant intra-arm fluctuations in SDS scores are <u>not</u> observed in the treatment period, the longitudinal plots can be supplemented by statistical tests (Wilcoxon/Mann-Whitney)[90] that compare mean levels of symptom distress across the entire treatment period. Again, the primary question of interest is whether the UFT+LV arm has significantly lower median symptom distress scores during treatment than the 5-FU+LV arm. If such differences are found, this would support a more detailed analysis of the specific symptoms that account for this difference. This general pattern of analysis will have to also be carried out on the individual items for which an additive score is not available (symptom-checklist and burden-of-care items).

18.2.5 <u>Missing Data</u>

Because of possible biases in comparing the UFT+LV and the 5-FU+LV arms, the following analytical techniques will be used to detect a missing data mechanism:

- Proportions of missing data in the two arms will be compared at each scheduled measurement time. The significance levels of the comparison will be assessed using simple tests of binomial proportions.

- If one or both arms have a large drop-off in QOL assessments at a given visit, the QOL scores for drop-offs as well as for those of the entire population will be examined for the previous visit. Such assessments may indicate that there were earlier reasons why some patients did not wish to complete the QOL study.

If no missing data mechanism can be detected, the data will be analyzed assuming the missing data are random. If a missing data mechanism appears to be present, we will employ the following strategies:

- Analyze QOL scores separately for each scheduled visit,
- Consider imputation procedures that model a missing data mechanism for performing repeated measures analysis.[96,97]

18.2.6 Sample Size and Statistical Power

Separate power analyses were carried out for each questionnaire (QA and QB), using the subscale or instrument with the most relevant information. Pilot data on colon cancer patients were provided by D. Cella for the FACT-C* and for other cancer patients using the 11-item SDS.** For purposes of stratification, it was assumed that age, sex and ethnicity in C-06 would be the same as in the NSAPB C-05 trial, i.e., male (55%), <59 years-old (50%), and nonwhite (13%).

In the case of the FACT-C, mean baseline scores for colon cancer patients, 79% of which were disease stage II or III, were 61.7 with a standard deviation of 13.7. We want to be able to detect at least a 10-point decline in the baseline QOL score. In order to be conservative, we calculated sample size estimates using a two-sided test and a Type I error = 0.01. This analysis indicates that we would require at least 90 subjects in each trial arm in order to have a 90% chance of detecting a clinically significant change of 10 points in the FACT-C.

With regard to the 11-item SDS, the SWOG cancer patient data indicate that we can expect to get baseline scores of approximately 16 with a standard deviation of 6.5. With regard to the SDS, Moinpour has suggested that a change of approximately one-half standard deviation from baseline should be considered clinically significant. For this

*Cella DF, personal communication, 1995.

**Moinpour C, personal communication, 1996.

study, we would like to be able to detect at least a 5-point increase in symptom distress scores over baseline. Using a two-sided test and a Type I error = 0.01, we would require at least 100 patients in each arm in order to have a better than 90% chance of detecting a clinically significant difference of 5 points.

With regard to testing hypotheses concerning differences between the two trial arms at the 15-16 week point of treatment, sample sizes of 90-100 patients in each arm would provide a better than 80% chance of detecting differences of 3 points on the SDS and 5 points on the FACT-C, assuming a Type I error rate = 0.05 and a two-sided test of hypotheses.

This analysis suggests that we require 90-100 individuals in the smallest stratification group for which comparisons will be made. This group is the nonwhite patient group. Based on a total n=1452 and the recruitment history for the NSABP C-05 trial, we estimate that there will be approximately 94 nonwhite patients available in each treatment arm. The remaining four stratification groups are all white and include: males <60 years, females <60 years, males ≥ 60 years, and females ≥ 60 years. We propose to limit recruitment to 100 patients in each arm for these four remaining cells. This would provide us with a total sample for the QOL trial of n=988 patients. An attempt will be made to include all patients in the QOL component of the study until the completion of any one cohort, after which any patient eligible for that cohort will not be asked to participate in the QOL study. Experience with the C-05 trial suggests that the age-sex cells fill at approximately the same rate and, for this reason, we are not at this time proposing any specialized recruitment procedures. However, we will review both our power calculations and the recruitment to the different stratification groups after 500 patients have entered the trial. If we find an imbalance in our recruitment to the various stratification groups or discover that our current assumptions underestimate baseline standard deviations, we will have an opportunity to adjust our sample size and implement modified recruitment procedures.

18.3 Biological Markers Substudy

We plan to investigate the effect on time to recurrence and survival of the following biological markers: p53 status, thymidylate synthase intensity, allelic loss of 18q, proliferative index, and microsatellite instability. Our primary analysis will determine whether these markers, when considered as a group, can be used to divide the population of patients into high-risk and low-risk groups. Each of the five variables will be used in a proportional hazards model to

determine if high-risk and low-risk patients can be identified. For this purpose, the variables will be defined as binary. We estimate that blocks and slides will be available on two-thirds (968) of the patients entered on this study. The primary endpoint will be recurrence. Assuming an equal number of patients in each group, no treatment effect, and an $\alpha = .05$ two-sided test, we estimate a statistical power of .92 to detect a reduction in the hazard rate for recurrence that is equivalent to a 10% absolute difference in the 5-year recurrence rate for the high- and low-risk groups at 5 years. Based on data from Protocol C-04, we estimate that the probability of recurrence 5 years after randomization will be 28%. Therefore, conservatively using a 5-year recurrence-free survival for the whole group of .72, we would expect the high- and low-risk groups to have recurrence-free survivals of .67 and .77, respectively (assuming equal sample sizes). If tests are conducted for each of the five markers separately at $\alpha = .01$ to adjust for multiple comparisons, the power would be .78 to detect a 10% difference in the 5-year recurrence rate for each marker. If we consider a treatment effect where UFT may have a $\pm$ 10% difference in recurrence (resulting in a change in the recurrence rate and hazard rate across the study), we estimate the power may be as low as .89 for the markers considered as a group and .73 for an individual marker. In addition, for individual variables, if the proportion of high-risk and low-risk patients is highly unequal, the statistical power will be lower. Because of its potential biological implications, we will also investigate whether or not relative treatment efficiency differs in low- and high-risk patients, but such analyses are limited by low statistical power of tests for interactions and an elevated false rejection rate due to multiple comparisons.

57312

Form QOLA (1/29/97)
C06_A_13

VERSION A

QUALITY OF LIFE QUESTIONNAIRE
NSABP PROTOCOL C-06

Instructions

1. Please use a no. 2 pencil
2. Darken circle completely
3. Erase cleanly any marks you wish to change

Patient's Name: _____ (first 3 initials of last name)

Institution: _____

Study Number: 2 6

Date Form Completed: Month / Day / Year

date stamp

HQ use only

This questionnaire is being given at:
(choose alternative for one arm only)

UFT+LV

- ○ baseline (with Version B)
- ○ day 1, cycle 2
- ○ day 1, cycle 3
- ○ day 1, cycle 4 (with Version B)
- ○ day 1, cycle 5
- ○ 1 year follow-up (with Version B)

5-FU+LV

- ○ baseline (with Version B)
- ○ day 1, cycle 2
- ○ day 1, cycle 3 (with Version B)
- ○ 1 year follow-up (with Version B)

Please Do Not Photocopy - Request Additional Copies from the NSABP Biostatistical Center

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

INSTRUCTIONS (ITEMS 1-13)

Each of the following items lists five different statements. Think about what each statement says and color in the dot on the left that corresponds to the statement that most closely indicates how you have been feeling during the past 7 days, including today. Please color in only one dot for each question. If you had no pai or nausea over the past week, please color in the first dot (mild/very mild) in items and 6.

1. NAUSEA (1)

○ I seldom feel any nausea at all.
○ I am nauseous once in a while.
○ I am often nauseous.
○ I am usually nauseous.
○ I suffer from nausea almost continually.

2. NAUSEA (2)

○ When I do have nausea, it is very mild.
○ When I do have nausea, it is mildly distressing.
○ When I have nausea, I feel pretty sick.
○ When I have nausea, I feel very sick.
○ When I have nausea, I am as sick as I could possibly be.

3. APPETITE

○ I have my normal appetite.
○ My appetite is usually, but not always, pretty good.
○ I don't really enjoy my food like I used to.
○ I have to force myself to eat my food.
○ I cannot stand the thought of food.

4. INSOMNIA

○ I sleep as well as I always have.
○ I have occasional spells of sleeplessness.
○ I frequently have trouble getting to sleep and staying asleep.
○ I have difficulty sleeping almost every night.
○ It is almost impossible for me to get a decent night's sleep.

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

5. PAIN (1)

- ○ I almost never have pain.
- ○ I have pain once in a while.
- ○ I frequently have pain several times a week.
- ○ I am usually in some degree of pain.
- ○ I am in some degree of pain almost constantly.

6. PAIN (2)

- ○ When I do have pain, it is very mild.
- ○ When I do have pain, it is mildly distressing.
- ○ The pain I do have is usually fairly intense.
- ○ The pain I have is usually very intense.
- ○ The pain I have is almost unbearable.

7. FATIGUE

- ○ I am usually not tired at all.
- ○ I am occasionally rather tired.
- ○ There are frequently periods when I am quite tired.
- ○ I am usually very tired.
- ○ Most of the time, I feel exhausted.

8. BOWEL

- ○ I have my normal bowel pattern.
- ○ My bowel pattern occasionally causes me some concern and discomfort.
- ○ I frequently have discomfort from my present bowel pattern.
- ○ I am usually in discomfort because of my present bowel pattern.
- ○ My present bowel pattern has changed drastically from what was normal for me.

HQ use only ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ 11 ○ 12

9. CONCENTRATION

- ○ I have my normal ability to concentrate.
- ○ I occasionally have trouble concentrating.
- ○ I often have trouble concentrating.
- ○ I usually have at least some difficulty concentrating.
- ○ I just can't seem to concentrate at all.

10. APPEARANCE

- ○ My appearance has basically not changed.
- ○ My appearance has gotten a little worse.
- ○ My appearance is definitely worse than it used to be, but I am not greatly concerned about it.
- ○ My appearance is definitely worse than it used to be, and I am concerned about it.
- ○ My appearance has changed drastically from what it was.

11. BREATHING

- ○ I usually breathe normally.
- ○ I occasionally have trouble breathing.
- ○ I often have trouble breathing.
- ○ I can hardly ever breathe as easily as I want.
- ○ I almost always have severe trouble with my breathing.

12. OUTLOOK

- ○ I am not fearful or worried.
- ○ I am a little worried about things.
- ○ I am quite worried, but unafraid.
- ○ I am worried and a little frightened about things.
- ○ I am worried and scared about things.

13. COUGH

- ○ I seldom cough.
- ○ I have an occasional cough.
- ○ I often cough.
- ○ I often cough and occasionally have severe coughing spells.
- ○ I often have persistent and severe coughing spells.

HQ use only ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ 11 ○ 12

INSTRUCTIONS (ITEMS 14-30)

Please indicate how much you have been bothered by each of the following problems during the past 7 days. Please color in only one dot for each problem.

	not at all	a little bit	some-what	quite a bit	very much
. Diarrhea	0 ○	1 ○	2 ○	3 ○	4 ○
. Abdominal pain or cramping	0 ○	1 ○	2 ○	3 ○	4 ○
. Gas pain	0 ○	1 ○	2 ○	3 ○	4 ○
. Mouth sores	0 ○	1 ○	2 ○	3 ○	4 ○
. Vomiting	0 ○	1 ○	2 ○	3 ○	4 ○
. Constipation	0 ○	1 ○	2 ○	3 ○	4 ○
. Skin problems (rash, irritation, redness)	0 ○	1 ○	2 ○	3 ○	4 ○
. Skin redness or peeling on hands and feet	0 ○	1 ○	2 ○	3 ○	4 ○
2. Fever or shivering (shaking, chills)	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ⊙8 ○9 ○10 ○11 ○12

	not at all	a little bit	some-what	quite a bit	very much
23. Numbness or tingling in the hands or feet	0 ○	1 ○	2 ○	3 ○	4 ○
24. Hair loss	0 ○	1 ○	2 ○	3 ○	4 ○
25. Chest pain	0 ○	1 ○	2 ○	3 ○	4 ○
26. Shortness of breath	0 ○	1 ○	2 ○	3 ○	4 ○
27. Pain at intravenous (I.V.) site	0 ○	1 ○	2 ○	3 ○	4 ○
28. Eye problems (irritation or redness)	0 ○	1 ○	2 ○	3 ○	4 ○
29. Hearing problems (ringing in ears)	0 ○	1 ○	2 ○	3 ○	4 ○
30. Other problems	0 ○	1 ○	2 ○	3 ○	4 ○

Please specify other problems:

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

57312

INSTRUCTIONS (ITEMS 31-33)

During the past month, how would you describe your experience with your treatment. Please color in only one dot for each statement.

31. Receiving treatment is convenient for me.

- ○ not at all
- ○ a little bit
- ○ somewhat
- ○ quite a bit
- ○ very much
- ○ I am not currently receiving treatment

32. My treatment has disrupted my life.

- ○ not at all
- ○ a little bit
- ○ somewhat
- ○ quite a bit
- ○ very much
- ○ I am not currently receiving treatment

33. I am satisfied with my current treatment.

- ○ not at all
- ○ a little bit
- ○ somewhat
- ○ quite a bit
- ○ very much
- ○ I am not currently receiving treatment

Thank You For Your Time In Completing This Questionnaire

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

57075

Form QOLB (1/29/97)
C06_B_V5

VERSION B

QUALITY OF LIFE QUESTIONNAIRE
NSABP PROTOCOL C-06

Instructions

1. Please use a no. 2 pencil
2. Darken circle completely
3. Erase cleanly any marks you wish to change

right ● wrong

Patient's Name: ______________________ [| |] first 3 initials of last name

Institution: ______________________

Study Number:

26

0	○○	0	○○○○○○○○
1	○○	1	○○○○○○○○
2	●○	2	○○○○○○○○
3	○○	3	○○○○○○○○
4	○○	4	○○○○○○○○
5	○○	5	○○○○○○○○
6	○●	6	○○○○○○○○
7	○○	7	○○○○○○○○
8	○○	8	○○○○○○○○
9	○○	9	○○○○○○○○

Date Form Completed:

	Month	Day	Year
0	○○	○○	○○
1	○○	○○	○○
2	○○	○○	○○
3	○○	○○	○○
4	○○	○○	○○
5	○○	○○	○○
6	○○	○○	○○
7	○○	○○	○○
8	○○	○○	○○
9	○○	○○	○○

date stamp

HQ use only

This questionnaire is being given at:
(choose alternative for one arm only)

UFT+LV

○ baseline (with Version A)
○ day 1, cycle 4 (with Version A)
○ 1 year follow-up (with Version A)

5-FU+LV

○ baseline (with Version A)
○ day 1, cycle 3 (with Version A)
○ 1 year follow-up (with Version A)

Please Do Not Photocopy - Request Additional Copies from the NSABP Biostatistical Center

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

57075

INSTRUCTIONS

Please indicate how true each statement has been for you during the past 7 days. Please color in only one dot for each statement.

	not at all	a little bit	some-what	quite a bit	very much
1. I have a lack of energy.	0 ○	1 ○	2 ○	3 ○	4 ○
2. I have nausea.	0 ○	1 ○	2 ○	3 ○	4 ○
3. Because of my physical condition, I have trouble meeting the needs of my family.	0 ○	1 ○	2 ○	3 ○	4 ○
4. I have pain.	0 ○	1 ○	2 ○	3 ○	4 ○
5. I am bothered by side effects of treatment.	0 ○	1 ○	2 ○	3 ○	4 ○
6. I feel ill.	0 ○	1 ○	2 ○	3 ○	4 ○
7. I am forced to spend time in bed.	0 ○	1 ○	2 ○	3 ○	4 ○
8. I feel distant from my friends.	0 ○	1 ○	2 ○	3 ○	4 ○
9. I get emotional support from my family.	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

57075

Please indicate how true each statement has been for you <u>during the past 7 days</u>.

	not at all	a little bit	some-what	quite a bit	very much
10. I get support from my friends and neighbors.	0 ○	1 ○	2 ○	3 ○	4 ○
11. My family has accepted my illness.	0 ○	1 ○	2 ○	3 ○	4 ○
12. Family communication about my illness is poor.	0 ○	1 ○	2 ○	3 ○	4 ○
13. I feel close to my partner (or the person who is my main support).	0 ○	1 ○	2 ○	3 ○	4 ○
14. I have confidence in my doctor(s).	0 ○	1 ○	2 ○	3 ○	4 ○
15. My doctor is available to answer my questions.	0 ○	1 ○	2 ○	3 ○	4 ○
16. I feel sad.	0 ○	1 ○	2 ○	3 ○	4 ○
17. I am proud of how I'm coping with my illness.	0 ○	1 ○	2 ○	3 ○	4 ○
18. I am losing hope in the fight against my illness.	0 ○	1 ○	2 ○	3 ○	4 ○
19. I feel nervous.	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Please indicate how true each statement has been for you <u>during the past 7 days</u>.

	not at all	a little bit	some-what	quite a bit	very much
20. I worry about dying.	0 ○	1 ○	2 ○	3 ○	4 ○
21. I worry that my condition will get worse.	0 ○	1 ○	2 ○	3 ○	4 ○
22. I am able to work (include work in home).	0 ○	1 ○	2 ○	3 ○	4 ○
23. My work (include work in home) is fulfilling.	0 ○	1 ○	2 ○	3 ○	4 ○
24. I am able to enjoy life.	0 ○	1 ○	2 ○	3 ○	4 ○
25. I have accepted my illness.	0 ○	1 ○	2 ○	3 ○	4 ○
26. I am sleeping well.	0 ○	1 ○	2 ○	3 ○	4 ○
27. I am enjoying the things I usually do for fun.	0 ○	1 ○	2 ○	3 ○	4 ○
28. I am content with the quality of my life right now.	0 ○	1 ○	2 ○	3 ○	4 ○
29. I have swelling or cramps in my stomach area.	0 ○	1 ○	2 ○	3 ○	4 ○
30. I am losing weight.	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Please indicate how true each statement has been for you <u>during the past 7 days</u>.

	not at all	a little bit	some-what	quite a bit	very much
31. I have control of my bowels.	0 ○	1 ○	2 ○	3 ○	4 ○
32. I can digest my food well.	0 ○	1 ○	2 ○	3 ○	4 ○
33. I have diarrhea.	0 ○	1 ○	2 ○	3 ○	4 ○
34. I have a good appetite.	0 ○	1 ○	2 ○	3 ○	4 ○
35. I like the appearance of my body.	0 ○	1 ○	2 ○	3 ○	4 ○

36. Have you been sexually active during the past year? ○ **yes** ○ **no**

37. If yes: I am satisfied with my sex life.	0 ○	1 ○	2 ○	3 ○	4 ○

For each question, please give the one answer the comes closest to the way you have been feeling <u>during the past 7 days</u>.

38. Did you feel full of pep?

- ○ all of the time
- ○ most of the time
- ○ a good bit of the time
- ○ some of the time
- ○ a little of the time
- ○ none of the time

HQ use only ○ **1** ○ **2** ○ **3** ○ **4** ○ **5** ○ **6** ○ **7** ○ **8** ○ **9** ○ **10** ○ **11** ○ **12**

For each question, please give the one answer the comes closest to the way you have been feeling <u>during the past 7 days</u>.

39. Did you have a lot of energy?

- ○ all of the time
- ○ most of the time
- ○ a good bit of the time
- ○ some of the time
- ○ a little of the time
- ○ none of the time

40. Did you feel worn out?

- ○ all of the time
- ○ most of the time
- ○ a good bit of the time
- ○ some of the time
- ○ a little of the time
- ○ none of the time

41. Did you feel tired?

- ○ all of the time
- ○ most of the time
- ○ a good bit of the time
- ○ some of the time
- ○ a little of the time
- ○ none of the time

HQ use only ○ **1** ○ **2** ○ **3** ○ **4** ○ **5** ○ **6** ○ **7** ○ **8** ○ **9** ○ **10** ○ **11** ○ **12**

42. As of today, to what extent have you resumed all your normal activities (both inside and outside the home and at work, if employed?)

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
○	○	○	○	○	○	○	○	○	○	○

43. Please score your overall quality of life during the past 7 days on a 10-point scale between death and perfect health.

death	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	perfect
	○	○	○	○	○	○	○	○	○	○	○	health

Thank You For Your Time In Completing This Questionnaire

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

Form QOLA-S (10/20/97)
C06_A_SPAN3

VERSION A

CUESTIONARIO DE LA CALIDAD DE VIDA
PROTOCOLO NSABP C-06

Instrucciones

1. **Favor de usar lápiz del número 2**
2. **Obscurezca el punto completamente**
3. **Borre limpiamente cualquier marca(s) que usted desee cambiar**

correcto **incorrecto**

Nombre del paciente: _____

primeras tres iniciales del apellido

Institución _____

Número del Estudio:

2 6

0	○○	0
1	○○	1
2	●	2
3	○○	3
4	○○	4
5	○○	5
6	○	6
7	○○	7
8	○○	8
9	○○	9

Fecha en que se Completó la Forma:

	Mes	Día	Año
0	○○	○○	○○
1	○○	○○	○○
2	○○	○○	○○
3	○○	○○	○○
4	○○	○○	○○
5	○○	○○	○○
6	○○	○○	○○
7	○○	○○	○○
8	○○	○○	○○
9	○○	○○	○○

Este cuestionario se está dando en:
(escoja la alternativa para un brazo solamente)

UFT+LV

- ○ línea basal (con la Versión B)
- ○ día 1, ciclo 2
- ○ día 1, ciclo 3
- ○ día 1, ciclo 4 (con la Versión B)
- ○ día 1, ciclo 5
- ○ seguimiento de 1 año (con la Versión B)

5-FU+LV

- ○ línea basal, (con la Versión B)
- ○ día 1, ciclo 2
- ○ día 1, ciclo 3 (con la Versión B)
- ○ seguimiento de 1 año (con la Versión B)

Favor De No Fotocopiar - Solicite Copias Adicionales Del Centro Biostático Del NSABP

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

INSTRUCCIONES (ARTICULOS DEL 1 AL 13)
Cada uno de los artículos siguientes lista cinco afirmaciones diferentes. Piense sobre lo que dice una de las afirmaciones y coloree en el punto en la izquierda que corresponda a la afirmación que indique más fielmente cómo se ha estado sintiendo usted durante los 7 (siete) días pasados, incluyendo hoy. Favor de colorear solamente en un punto para cada pregunta. Si usted no tuvo dolor ni náusea durante la semana pasada, favor de colorear en el primer punto (leve/muy leve) en los articulos 2 y 6.

1. NÁUSEA (1)

○ Raras veces tengo náusea.
○ De vez en cuando tengo náusea.
○ Frecuentemente tengo náusea.
○ Al menos la mitad del tiempo tengo náusea.
○ Casi continuamente tengo náusea.

2. NÁUSEA (2)

○ Cuando tengo náusea, es muy leve.
○ Cuando tengo náusea, es una molestia leve.
○ Cuando tengo náusea, me siento muy enfermo.
○ Cuando tengo náusea, generalmente me siento bastante enfermo.
○ Cuando tengo náusea, me siento extremadamente enfermo.

3. APETITO

○ Mi apetito es normal y me agrada la buena comida.
○ Usualmente mi apetito es bueno pero no siempre.
○ En realidad no me agrada la comida.
○ Tengo que forzarme para comer.
○ No puedo soportar el pensar en la comida.

4. INSOMNIO (Dificultad para Dormir)

○ Duermo tan bien como siempre.
○ Ocasionalmente tengo problemas para dormir y permanecer dormido.
○ Frecuentemente tengo problemas para dormir.
○ Tengo problemas para dormir y permanecer dormido casi todas las noches.
○ Es casi imposible que yo duerma una buena noche.

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

5. DOLOR (1)

○ Casi nunca tengo dolor.
○ Tengo dolor de vez en cuando.
○ Tengo dolor varias veces a la semana.
○ Generalmente tengo algo de dolor.
○ Me siento con dolor casi constantemente.

6. DOLOR (2)

○ Cuando tengo dolor no me molesta casi nada.
○ Cuando tengo dolor me molesta un poco.
○ Cuando tengo dolor es moderadamente intenso.
○ El dolor que tengo es muy intenso.
○ El dolor que tengo es casi insoportable.

7. FATIGA

○ Raramente me siento cansado o fatigado.
○ Hay veces que me siento algo cansado o fatigado.
○ Hay veces que me siento muy cansado y fatigado.
○ Usualmente estoy muy cansado y fatigado.
○ La mayor parte del tiempo estoy exhausto.

8. REGULARIDAD INTESTINAL (Problemas con la Frecuencia o Dolor Durante los Movimientos Intestinales)

○ Mis movimientos intestinales son normales.
○ Mis movimientos intestinales ocasionalmente me causan algo de incomodidad.
○ Mis movimientos intestinales ocasionalmente me causan bastante molestia o incomodidad.
○ Con frecuencia estoy muy molesto o incómodo por mis movimientos intestinales.
○ Casi siempre estoy molesto e incómodo por mis movimientos intestinales.

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

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9. CONCENTRACIÓN

- ○ Tengo habilidad normal para concentrarme.
- ○ Ocasionalmente tengo problemas para concentrarme.
- ○ Ocasionalmente tengo bastante problemas para concentrarme.
- ○ Usualmente tengo bastante problemas para concentrarme.
- ○ Parece que no me puedo concentrar en nada.

10. APARIENCIA

- ○ Básicamente mi apariencia no ha cambiado.
- ○ Ocasionalmente me preocupa que empeore mi apariencia física.
- ○ Frecuentemente me preocupa que mi apariencia física este empeorando.
- ○ La mayor parte del tiempo me preocupa que mi apariencia física este empeorando.
- ○ El deterioro de mi apariencia física me preocupa constantemente.

11. RESPIRACIÓN

- ○ Usualmente respiro normal.
- ○ Ocasionalmente tengo problemas para respirar.
- ○ Frecuentemente tengo problemas para respirar.
- ○ Casi nunca puedo respirar con la facilidad que quiero.
- ○ Casi siempre tengo severos problemas con mi respiración.

12. PERCEPCIÓN/PERSPECTIVA

- ○ No estoy (me siento) temeroso o preocupado.
- ○ Estoy un poco preocupado de las cosas
- ○ Estoy muy preocupado pero no tengo miedo.
- ○ Estoy preocupado y un poco temeroso de las cosas.
- ○ Estoy preocupado y temeroso de las cosas.

13. TOS

- ○ Nunca o casi nunca toso.
- ○ Toso ocasionalmente.
- ○ Toso con frecuencia.
- ○ Toso con frecuencia y a veces tengo severos ataques de tos.
- ○ Con frecuencia tengo severos y persistentes ataques de tos.

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

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INSTRUCCIONES (ARTICULOS DEL 14 AL 30)
Favor de indicar cuánto ha sido molestado(a) por cada uno de los problemas siguientes durante los 7 dias pasados. Favor de colorear solamente en un punto para cada problema.

	nada	un poco	algo	bastante	mucho
14. Diarrea	0 ○	1 ○	2 ○	3 ○	4 ○
15. Dolor o calambres del abdomen	0 ○	1 ○	2 ○	3 ○	4 ○
16. Dolor por gas	0 ○	1 ○	2 ○	3 ○	4 ○
17. Ulceras de la boca	0 ○	1 ○	2 ○	3 ○	4 ○
18. Vómito	0 ○	1 ○	2 ○	3 ○	4 ○
19. Estreñimiento/ Constipación	0 ○	1 ○	2 ○	3 ○	4 ○
20. Problemas de la piel (salpullido, irritación, enrojecimiento)	0 ○	1 ○	2 ○	3 ○	4 ○
21. Enrojecimiento de la piel o descamación en las manos y los pies	0 ○	1 ○	2 ○	3 ○	4 ○
22. Fiebre o estremecimiento (temblor, escalofrios.)	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

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	nada	un poco	algo	bastante	mucho
23. Entumecimiento u hormigueo de las manos o de los pies	0 ○	1 ○	2 ○	3 ○	4 ○
24. Pérdida del cabello	0 ○	1 ○	2 ○	3 ○	4 ○
25. Dolor torácico (del pecho)	0 ○	1 ○	2 ○	3 ○	4 ○
26. Corto de respiración	0 ○	1 ○	2 ○	3 ○	4 ○
27. Dolor en el lugar de la canalización intravenosa (I.V.)	0 ○	1 ○	2 ○	3 ○	4 ○
28. Problemas de los ojos (irritación o enrojecimiento)	0 ○	1 ○	2 ○	3 ○	4 ○
29. Problemas de la audición (zumbido en los oidos)	0 ○	1 ○	2 ○	3 ○	4 ○
30. Otros problemas	0 ○	1 ○	2 ○	3 ○	4 ○

Favor de especificar otros problemas:

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

INSTRUCCIONES (ARTICULOS DEL 31 AL 33)
Durante el mes pasado, cómo describiría su experiencia con su tratamiento. Favor de colorear en un punto solamente para cada afirmación.

31. Recibir el tratamiento es conveniente para mí.

○ nada
○ un poco
○ algo
○ bastante
○ mucho
○ Yo no estoy recibiendo tratamiento actualmente

32. Mi tratamiento ha desbaratado mi vida.

○ nada
○ un poco
○ algo (de alguna manera)
○ bastante
○ mucho
○ Yo no estoy recibiendo tratamiento actualmente

33. Yo estoy satisfecho con mi tratamiento actual.

○ nada
○ un poco
○ algo
○ bastante
○ mucho
○ Yo no estoy recibiendo tratamiento actualmente

Gracias Por Su Tiempo Para Completar Este Cuestionario

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

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Form QOLB-S (10/20/97)
C06_B_SPAN3

VERSION B

CUESTIONARIO DE LA CALIDAD DE VIDA

PROTOCOLO NSABP C-06

Instrucciones

1. **Favor de usar lápiz del número 2**
2. **Obscurezca el punto completamente**
3. **Borre limpiamente cualquier marca(s) que usted desee cambiar**

Nombre del Paciente:_____ **primeras 3 iniciales del apellido**

Institución:_____

Número del Estudio: 2 6

Fecha en que se Completó la Forma: Mes Día Año

Este cuestionario se está dando en:
(escoja la alternativa para un brazo solamente)

UFT+LV

- ○ línea basal (con la Versión A)
- ○ día 1, ciclo 4 (con la Versión A)
- ○ seguimiento de 1 año (con la Versión A)

5-FU+LV

- ○ línea basal (con la Versión A)
- ○ día 1, ciclo 3 (con la Versión A)
- ○ seguimiento de 1 año (con la Versión A)

Favor De No Fotocopiar - Solicite Copias Adicionales del Centro Biostático NSABP

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

INSTRUCCIONES

Favor de indicar qué tan verdadero ha sido para usted cada afirmación durante los 7 días pasados. Favor de colorear solamente en uno de los puntos para cada afirmación.

	nada	un poco	algo	bastante	mucho
1. Me siento débil.	0 ○	1 ○	2 ○	3 ○	4 ○
2. Tengo náusea.	0 ○	1 ○	2 ○	3 ○	4 ○
3. Tengo dificultad para cumplir mis obligaciones familiares, debido a mi enfermedad.	0 ○	1 ○	2 ○	3 ○	4 ○
4. Tengo dolor.	0 ○	1 ○	2 ○	3 ○	4 ○
5. Me molestan los efectos secundarios del tratamiento.	0 ○	1 ○	2 ○	3 ○	4 ○
6. Me siento enfermo(a).	0 ○	1 ○	2 ○	3 ○	4 ○
7. Necesito estar acostado(a).	0 ○	1 ○	2 ○	3 ○	4 ○
8. Me siento alejado(a) de mis amistades.	0 ○	1 ○	2 ○	3 ○	4 ○
9. Recibo apoyo emocional de mi familia.	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

Favor de incidar qué tan verdadero ha sido para usted cada afirmación durante los 7 días pasados.

	nada	un poco	algo	bastante	mucho
10. Recibo apoyo de mis amistades y vecinos.	0 ○	1 ○	2 ○	3 ○	4 ○
11. Mi familia ha aceptado mi enfermedad.	0 ○	1 ○	2 ○	3 ○	4 ○
12. En mi familia la comunicación sobre mi enfermedad es mala.	0 ○	1 ○	2 ○	3 ○	4 ○
13. Me siento cercano(a) a mi pareja (o a la persona que me da apoyo).	0 ○	1 ○	2 ○	3 ○	4 ○
14. Tengo confianza en mi(s) doctor(es).	0 ○	1 ○	2 ○	3 ○	4 ○
15. Mi(s) doctor(es) está(n) disponible(s) para contestar mis preguntas.	0 ○	1 ○	2 ○	3 ○	4 ○
16. Me siento triste.	0 ○	1 ○	2 ○	3 ○	4 ○
17. Me siento orgulloso(a) de como estoy enfrentando mi enfermedad.	0 ○	1 ○	2 ○	3 ○	4 ○
18. Estoy perdiendo las esperanzas en la lucha contra mi enfermedad.	0 ○	1 ○	2 ○	3 ○	4 ○
19. Me siento nervioso(a).	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

Favor de indicar qué tan verdadero ha sido para usted cada afirmación durante los 7 días pasados.

	nada	un poco	algo	bastante	mucho
20. Me preocupa morir.	0 ○	1 ○	2 ○	3 ○	4 ○
21. Me preocupa que mi enfermedad empeore.	0 ○	1 ○	2 ○	3 ○	4 ○
22. Puedo trabajar (incluya trabajo en el hogar).	0 ○	1 ○	2 ○	3 ○	4 ○
23. Me satisface mi trabajo (incluya trabajo en el hogar.)	0 ○	1 ○	2 ○	3 ○	4 ○
24. Puedo disfrutar la vida.	0 ○	1 ○	2 ○	3 ○	4 ○
25. He aceptado mi enfermedad.	0 ○	1 ○	2 ○	3 ○	4 ○
26. Duermo bien.	0 ○	1 ○	2 ○	3 ○	4 ○
27. Disfruto mis pasatiempos de siempre.	0 ○	1 ○	2 ○	3 ○	4 ○
28. Estoy contento(a) con mi vida (calidad de vida) actual.	0 ○	1 ○	2 ○	3 ○	4 ○
29. Tengo hichazón o calambres en el area del estómago.	0 ○	1 ○	2 ○	3 ○	4 ○
30. Estoy bajando de peso.	0 ○	1 ○	2 ○	3 ○	4 ○

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

Favor de indicar qué tan verdadero ha sido para usted cada afirmación durante los 7 días pasados.

	nada	un poco	algo	bastante	mucho
31. Tengo control de mis evacuaciones intestinales.	0 ○	1 ○	2 ○	3 ○	4 ○
32. Puedo digerir bien mis alimentos.	0 ○	1 ○	2 ○	3 ○	4 ○
33. Tengo diarrea.	0 ○	1 ○	2 ○	3 ○	4 ○
34. Tengo buen apetito.	0 ○	1 ○	2 ○	3 ○	4 ○
35. Me gusta mi apariencia personal.	0 ○	1 ○	2 ○	3 ○	4 ○

36. Ha estado usted activo(a) sexualmente durante el último año? ○ **si** ○ **no**

37. Si: Estoy satisfecho(a) con mi vida sexual.	0 ○	1 ○	2 ○	3 ○	4 ○

Por cada pregunta, favor de indicar la respuesta que más se acerca a la manera como se ha sentido usted durante los 7 días pasados.

38. Se ha sentido llena de vida?

○ todo el tiempo
○ la mayor parte del tiempo
○ gran parte del tiempo
○ parte del tiempo
○ una pequeña parte del tiempo
○ en ningún momento

HQ use only ○ **1** ○ **2** ○ **3** ○ **4** ○ **5** ○ **6** ○ **7** ○ **8** ○ **9** ○ **10** ○ **11** ○ **12**

Por cada pregunta, favor de indicar la respuesta que más se acerca a la manera como se ha sentido usted durante los 7 días pasados.

39. Ha tenido mucha energía?

- ○ todo el tiempo
- ○ la mayor parte del tiempo
- ○ gran parte del tiempo
- ○ parte del tiempo
- ○ una pequeña parte del tiempo
- ○ en ningún momento

40. Se ha sentido agotada?

- ○ todo el tiempo
- ○ la mayor parte del tiempo
- ○ gran parte del tiempo
- ○ parte del tiempo
- ○ una pequeña parte del tiempo
- ○ en ningún momento

41. Se ha sentido cansada?

- ○ todo el tiempo
- ○ la mayor parte del tiempo
- ○ gran parte del tiempo
- ○ parte del tiempo
- ○ una pequeña parte del tiempo
- ○ en ningún momento

HQ use only ○ **1** ○ **2** ○ **3** ○ **4** ○ **5** ○ **6** ○ **7** ○ **8** ○ **9** ○ **10** ○ **11** ○ **12**

42. Hasta ahora, hasta que grado ha reanudado/continuado usted todas sus actividades normales (ambas adentro y afuera del hogar y en el trabajo, si está empleado[a])?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
○	○	○	○	○	○	○	○	○	○	○

43. Favor de dar una calificacion a su calidad de vida total durante los 7 días pasados en una escala de 10 puntos entre la muerte y la salud perfecta.

	0	1	2	3	4	5	6	7	8	9	10	
muerte	○	○	○	○	○	○	○	○	○	○	○	salud perfecta

Gracias Por Su Tiempo
En Completar Este Cuestionario

HQ use only ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

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VERSION A
Questionnaire sur la qualité de vie
Protocole NSABP C-06

Instructions

1. *Utlisez un crayon à mine #2*
2. *Noircir complètement le cercle*
3. *Effacer proprement toutes les marques que vous désirez changer*

bonne façon **mauvaise façon**

Nom du patient: _____ ☐☐☐

3 premières lettres du nom de famille

Institution: _____

Numéro d'Etude:

2 6 ☐☐☐☐☐☐☐

0	○○	0 ○○○○○○○
1	○○	1 ○○○○○○○
2	●○	2 ○○○○○○○
3	○○	3 ○○○○○○○
4	○○	4 ○○○○○○○
5	○○	5 ○○○○○○○
6	○●	6 ○○○○○○○
7	○○	7 ○○○○○○○
8	○○	8 ○○○○○○○
9	○○	9 ○○○○○○○

Date où le formulaire est complété

	Mois ☐☐	Jour ☐☐	Annee ☐☐
0	○○	○○	○○
1	○○	○○	○○
2	○○	○○	○○
3	○○	○○	○○
4	○○	○○	○○
5	○○	○○	○○
6	○○	○○	○○
7	○○	○○	○○
8	○○	○○	○○
9	○○	○○	○○

Date

A l'usage de HQ

Ce questionnaire vous a été remis à la période suivante:
(faites votre choix pour seulement un des bras de traitements)

UFT+LV

- ○ Prétraitment (avec Version B)
- ○ Jour 1, cycle 2
- ○ Jour 1, cycle 3
- ○ Jour 1, cycle 4 (avec Version B)
- ○ Jour 1, cycle 5
- ○ Suivi à un an (avec Version B)

5-FU+LV

- ○ Prétraitement (avec Version B)
- ○ Jour 1, cycle 2
- ○ Jour 1, cycle 3 (avec Version B)
- ○ Suivi à un an (avec Version B)

S.V.P. Ne pas photocopier - Demander au Centre de Biostatistique du NSABP des formulaires additionnels.

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

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INSTRUCTIONS (ITEMS 1-13)

Dans chacune des sections ci-dessoux, il y a 5 affirmations différentes. Réfléchissez à chacune des affirmations et noircissez le cercle correspondant à l'affirmation qui ressemble le plus à ce que vous avez ressenti au cours des sept derniers jours, en incluant aujourd'hui. Veuillez ne noircir qu'un seul cercle par question. Si vous n'avez pas eu de douleurs ou de nausées durant la dernière semaine, veuillez s'il vous plait noircir le premier cercle (léger/très léger) pour les sections 2 et 6.

1. NAUSEE (1)

○ Je ne ressens à peu près pas de nausée.
○ Je me sens nauséeux une fois de temps en temps.
○ J'ai souvent des nausées.
○ J'ai habituellement des nausées.
○ Je souffre de nausées presque continuellement.

2. NAUSEE (2)

○ Lorsque j'ai des nausées, c'est très léger.
○ Lorsque j'ai des nausées, c'est légèrement angoissant.
○ Lorsque j'ai des nausées, je me sens assez malade.
○ Lorsque j'ai des nausées, je me sens très malade.
○ Lorsque j'ai des nausées, je ne peux pas être plus malade que cela.

3. APPETIT

○ Mon appétit est comme d'habitude.
○ Mon apétit est habituellement assez bon.
○ Je n'apprécie pas ma nourriture comme a l'habitude.
○ Il faut que je me force pour manger.
○ J'ai le dédain total pour le nourriture.

4. INSOMNIE

○ Je dors aussi bien que d'habitude.
○ J'ai à l'occasion des périodes d'insomnie.
○ J'ai souvent de la difficulté à m'endormir et à rester endormi.
○ J'ai de la difficulté à dormir presqu'à chaque nuit.
○ C'est pratiquement impossible pour moi d'avoir une bonne nuit de sommeil.

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

5. DOULEUR (1)

- ○ Je n'ai presque jamais de douleur.
- ○ J'ai de la douleur de temps à autre.
- ○ J'ai de la douleur plusieurs fois par semaine.
- ○ J'éprouve habituellement de la douleur.
- ○ J'éprouve presque constamment de la douleur.

6. DOULEUR (2)

- ○ Quand j'ai de la douleur, c'est très léger.
- ○ Quand j'ai de la douleur, c'est légèrement ennuyeux.
- ○ Ma douleur est habituellement assez intense.
- ○ Ma douleur est habituellement très intense.
- ○ Ma douleur est presque intolérable.

7. FATIGUE

- ○ Habituellment je ne suis pas fatigué du tout.
- ○ A l'occasion je suis assez fatigué.
- ○ Il y a des périodes fréquentes où je me sens assez fatigué.
- ○ Je me sens habituellement très fatigué.
- ○ La plupart du temps, je me sens épuisé.

8. FONCTION INTESTINALE

- ○ Mes intestins fonctionnent normalement.
- ○ A l'occasion ma fonction intestinale me donne des soucis et de l'inconfort.
- ○ J'éprouve fréquemment des malaises intestinaux.
- ○ Ma fonction intestinale me cause habituellement l'inconfort.
- ○ Ma fonction intestinale actuelle s'est modifier de facon drastique.

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

9. CONCENTRATION

- ○ Je suis capable de me concentrer comme d'habitude.
- ○ J'ai occasionellement des problèmes de concentration.
- ○ J'ai souvent des problèmes de concentration.
- ○ J'ai habituellement certaines difficultés de concentration.
- ○ Il me semble que je ne peux pas me concentrer du tout.

10. APPARENCE

- ○ Mon apparence n'a practiquement pas changé.
- ○ Mon apparence s'est légèrement détérioré.
- ○ Mon apparence est définitivement pire que ce qu'elle était, mais je ne m'en soucie pas.
- ○ Mon apparence est définitivement pire que ce qu'elle était, et ça me rend soucieux.
- ○ Mon apparence a changé de façon drastique.

11. RESPIRATION

- ○ Je respire comme d'habitude.
- ○ J'ai occasionellement des problèmes à respirer.
- ○ J'ai souvent des problèmes respiratoires.
- ○ Je ne respire pas aussi bien que je le voudrais.
- ○ J'ai presque toujours des problèmes sévères avec ma respiration.

12. CONCEPTION DE LA VIE

- ○ Je n'ai pas peur ou je ne suis pas préoccupé.
- ○ Je suis légèrement préoccupé.
- ○ Je suis assez préoccupé, mais je n'ai pas peur.
- ○ Je suis préoccupé et légèrement appeuré.
- ○ Je suis préoccupé et effrayé.

13. TOUX

- ○ Je tousse rarement.
- ○ J'ai une toux occasionelle.
- ○ Je tousse souvent.
- ○ Je tousse souvent et a l'occasion j'ai des quintes de toux.
- ○ J'ai souvent des quintes de toux persistentes et sévères.

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

INSTRUCTIONS (ITEMS 14-30)

Veuillez indiquer combien vous avez été ennuyé par chacun des problèmes durant les 7 derniers jours. S'il vous plait noircir un seul cercle pour chacun des problèmes suivants.

	Pas du tout	Un petit peu	Quelque peu	Assez souvent	Beaucoup
14. Diarrhée	0 ○	1 ○	2 ○	3 ○	4 ○
15. Douleurs abdominales ou crampes	0 ○	1 ○	2 ○	3 ○	4 ○
16. Douleurs causées par des gas	0 ○	1 ○	2 ○	3 ○	4 ○
17. Plaies dans la bouche	0 ○	1 ○	2 ○	3 ○	4 ○
18. Vomissement	0 ○	1 ○	2 ○	3 ○	4 ○
19. Constipation	0 ○	1 ○	2 ○	3 ○	4 ○
20. Problèmes de peau (rash, irritation, rougeur)	0 ○	1 ○	2 ○	3 ○	4 ○
21. Rougeur de la peau ou pelage sur les mains et les peids	0 ○	1 ○	2 ○	3 ○	4 ○
22.	0 ○	1 ○	2 ○	3 ○	4 ○

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

	Pas du tout	Un petit peu	Quelque peu	Assez souvent	Beaucoup
23. Engourdissement ou picotement aux mains ou aux pieds	0 ○	1 ○	2 ○	3 ○	4 ○
24. Perte de cheveux	0 ○	1 ○	2 ○	3 ○	4 ○
25. Douleur thoracique	0 ○	1 ○	2 ○	3 ○	4 ○
26. Manque de souffle	0 ○	1 ○	2 ○	3 ○	4 ○
27. Douleurs à un site d'injection intraveineuse (I.V.)	0 ○	1 ○	2 ○	3 ○	4 ○
28.	0 ○	1 ○	2 ○	3 ○	4 ○
29. Problèmes auditifs (bourdonnement dans les oreilles)	0 ○	1 ○	2 ○	3 ○	4 ○
30. Autres problèmes	0 ○	1 ○	2 ○	3 ○	4 ○

S'il vous plait spécifier les autres problèmes:

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

INSTRUCTIONS (ITEMS 31-33)

Durant le dernier mois, comment décririez-vous votre expérience avec votre traitement. Veuillez s'il vous plait ne noircir qu'un cercle pour chaque affirmation.

31. Recevoir le traitement me convient.

- ○ pas du tout
- ○ un petit peu
- ○ quelque peu
- ○ assez bien
- ○ beaucoup
- ○ Je ne reçois présentement aucun traitement

32. Mon traitement a désorganisé ma vie.

- ○ pas du tout
- ○ un petit peu
- ○ quelque peu
- ○ assez bien
- ○ beaucoup
- ○ Je ne reçois présentement aucun traitement

33. Je suis satisfait avec le traitement actuel.

- ○ pas du tout
- ○ un petit peu
- ○ quelque peu
- ○ assez bien
- ○ beaucoup
- ○ Je ne reçois présentement aucun traitement

NOUS VOUS REMERCIONS D'AVOIR PRIS LE TEMPS DE COMPLETER CE QUESTIONNAIRE

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

VERSION B

Questionnaire sur la qualité de vie
PROTOCOLE NSABP C-06

Instructions

1. **Utiliser un crayon à mine #2**
2. **Noircir complètement le cercle**
3. **Effacer proprement toutes les marques que vous désirez changer**

bonne façon **mauvaise façon**

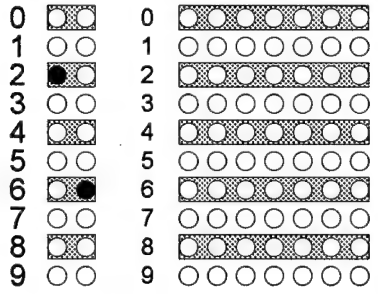
Nom du Patient: _____ | | |

3 premières lettres du nom de famille

Institution: _____

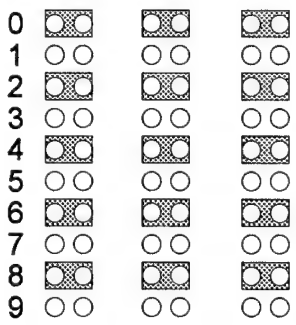
Numéro de l'étude:

2 6



Date où le formulaire est complété:

Mois	Jour	Année



Date

A l'usage de HQ

Ce questionnaire vous a été remis à la période suivante:
(faites votres choix pour seulement un des bras de traitements)

UFT+LV

○ Prétraitement (avec Version A)
○ Jour 1, cycle 4 (avec Version A)
○ Suivi à un an (avec Version A)

5-FU+LV

○ Prétraitement (avec Version A)
○ Jour 1, cycle 3 (avec Version A)
○ Suivi à un an (avec Version A)

S.V.P. ne pas photocopier - Demander au Centre de Biostatistique du NSABP des formulaires additionelles.

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

INSTRUCTIONS

S'il-vous-plaît, veuillez nous dire ce qui se rapproche le plus de la réalité à propos des affirmations suivantes au cours des sept derniers jours.
S'il-vous-plaît, ne noircir qu'un seul cercle par affirmation.

	Pas du tout	Quelque-fois	Régulièrement	Assez Souvent	Souvent
1. J'ai un manque d'énergie.	0 ○	1 ○	2 ○	3 ○	4 ○
2. J'ai des nausées.	0 ○	1 ○	2 ○	3 ○	4 ○
3. A cause de mon état physique, j'ai du mal à subvenir aux besoins de ma famille.	0 ○	1 ○	2 ○	3 ○	4 ○
4. J'ai de la douleur.	0 ○	1 ○	2 ○	3 ○	4 ○
5. Je suis ennuyé par les effets secondaires des traitements.	0 ○	1 ○	2 ○	3 ○	4 ○
6. Je me sens malade.	0 ○	1 ○	2 ○	3 ○	4 ○
7. Je suis obligé de prendre le lit.	0 ○	1 ○	2 ○	3 ○	4 ○
8. Je me sens éloigné de mes amis.	0 ○	1 ○	2 ○	3 ○	4 ○
9. Ma famille me supporte sur le plan émotif.	0 ○	1 ○	2 ○	3 ○	4 ○

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

Pour chaque question, veuillez s'il-vous-plaît noircir le cercle qui correspond le mieux à ce que vous avez ressenti au cours des sept derniers jours.

		Pas du tout	Un petit peu	Quelque peu	Assez souvent	Beaucoup
10.	Mes amis et mes voisins me supportent.	0 ○	1 ○	2 ○	3 ○	4 ○
11.	Ma famille a accepté ma maladie.	0 ○	1 ○	2 ○	3 ○	4 ○
12.	La communication avec ma famille au sujet de ma maladie est médiocre.	0 ○	1 ○	2 ○	3 ○	4 ○
13.	Je me sens près de mon conjoint (ou de la personne qui est mon soutien principal).	0 ○	1 ○	2 ○	3 ○	4 ○
14.	J'ai confiance en mon (mes) médecin(s).	0 ○	1 ○	2 ○	3 ○	4 ○
15.	Mon médecin est disponible pour répondre à mes questions.	0 ○	1 ○	2 ○	3 ○	4 ○
16.	Je me sens triste.	0 ○	1 ○	2 ○	3 ○	4 ○
17.	Je me sens fier(ère) de la façon à laquelle je fait face à ma maladie.	0 ○	1 ○	2 ○	3 ○	4 ○
18.	Je perds espoir dans la lutte contre ma maladie.	0 ○	1 ○	2 ○	3 ○	4 ○
19.	Je me sens nerveux(se)	0 ○	1 ○	2 ○	3 ○	4 ○

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

Pour chaque question, veuillez s'il-vous-plaît noircir le cercle qui correspond le mieux à ce que vous avez ressenti au cours des 7 derniers jours.

	Pas du tout	Un petit peu	Quelque peu	Assez souvent	Beaucoup
20. J'ai peur de mourir.	0 ○	1 ○	2 ○	3 ○	4 ○
21. J'ai peur que mon état se détériore	0 ○	1 ○	2 ○	3 ○	4 ○
22. Je suis capable de travailler (incluant le travail à la maison)	0 ○	1 ○	2 ○	3 ○	4 ○
23. Mon travail (incluant le travail à la maison) est satisfaisant.	0 ○	1 ○	2 ○	3 ○	4 ○
24. Je suis capable de profiter de la vie.	0 ○	1 ○	2 ○	3 ○	4 ○
25. J'ai accepté ma maladie.	0 ○	1 ○	2 ○	3 ○	4 ○
26. Je dors bien.	0 ○	1 ○	2 ○	3 ○	4 ○
27. J'aime faire les choses que je fais habituellement pour me distraire.	0 ○	1 ○	2 ○	3 ○	4 ○
28. Je suis présentement satisfait(e) de ma qualité de vie.	0 ○	1 ○	2 ○	3 ○	4 ○
29. J'ai du gonflement ou des crampes au niveau de l'estomac.	0 ○	1 ○	2 ○	3 ○	4 ○
30. Je perds du poids.	0 ○	1 ○	2 ○	3 ○	4 ○

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

Draft

Pour chaque question, veuillez s'il-vous-plaît noircir le cercle qui correspond le mieux à ce que vous avez ressenti au cours des 7 derniers jours.

	Pas du tout	Un petit peu	Quelque peu	Assez souvent	Beaucoup
31. J'ai le contrôle sur mes fonctions intestinales.	0 ○	1 ○	2 ○	3 ○	4 ○
32. Je digère bien la nourriture.	0 ○	1 ○	2 ○	3 ○	4 ○
33. J'ai de la diarrhée.	0 ○	1 ○	2 ○	3 ○	4 ○
34. J'ai un bon appétit.	0 ○	1 ○	2 ○	3 ○	4 ○
35. J'aime mon apparence corporelle.	0 ○	1 ○	2 ○	3 ○	4 ○

36. Avez-vous été actif sexuellement durant la dernière année? ○ **oui** ○ **non**

37. Si oui: Je suis satisfait(e) de ma vie sexuelle.	0 ○	1 ○	2 ○	3 ○	4 ○

Pour chaque question, veuillez s'il-vous-plaît noircir le cercle qui correspond le mieux à ce que vous avez ressenti au cours des 7 derniers jours.

38. Vous sentiez vous plein d'entrain?

- ○ toujours
- ○ la plupart du temps
- ○ une bonne partie du temps
- ○ quelquefois
- ○ durant peu de temps
- ○ jamais

A l'usage de HQ ○ **1** ○ **2** ○ **3** ○ **4** ○ **5** ○ **6** ○ **7** ○ **8** ○ **9** ○ **10** ○ **11** ○ **12**

Pour chaque question, veuillez s'il-vous-plaît noircir le cercle qui correspond le mieux à ce que vous avez ressenti au cours des 7 derniers jours.

39. Aviez-vous beaucoup d'énergie?

- ○ toujours
- ○ la plupart du temps
- ○ une bonne partie du temps
- ○ quelquefois
- ○ durant peu de temps
- ○ jamais

40. Vous sentiez-vous épuisé?

- ○ toujours
- ○ la plupart du temps
- ○ une bonne partie du temps
- ○ quelquefois
- ○ durant peu de temps
- ○ jamais

41. Vous sentiez-vous fatigué?

- ○ toujours
- ○ la plupart du temps
- ○ une bonne partie du temps
- ○ quelquefois
- ○ durant peu de temps
- ○ jamais

A l'usage de HQ ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ 11 ○ 12

42. A ce jour, jusqu'à quel point avez-vous repris vos activités normales (à l'intérieur comme a l'extérieur de la maison et au travail, si vous avez un emploi)?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
○	○	○	○	○	○	○	○	○	○	○

43. Veuillez s.v.p. noircir le cercle qui sur une échelle de dix points entre la mort et la santé parfaite correspond le plus à votre qualité de vie globale au cours des 7 derniers jours.

	0	1	2	3	4	5	6	7	8	9	10	
mort	○	○	○	○	○	○	○	○	○	○	○	parfaite sante

NOUS VOUS REMERCIONS D'AVOIR PRIS LE TEMPS DE COMPLETER CE QUESTIONNAIRE

A l'usage de HQ ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10 ○11 ○12

APPENDIX

i. Scannable Forms Report

REVIEW OF THE USE OF SCANNABLE QUALITY OF LIFE (QOL) FORMS ON NSABP STUDY C-06

1. BACKGROUND

a. **Current Scannable Form Software:** Teleform, Cardiff Software (Ver. 3 for Windows 3.1.1 and Ver. 4 for Windows 95).

b. **Current Hardware Configuration:** IBM-PC compatible computer, Cyrex 100 Mhz CPU (equivalent of 70-90Mhz Pentium); 32 Mb RAM, 1.3 Gb hard dive. HP 4C scanner with HP 50 page document reader.

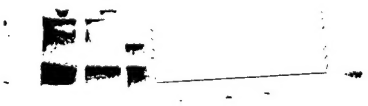
c. **Rationale for Use of Scannable Forms:** Self-administered NSC scannable forms have been relatively successful in the BCPT. They have been acceptable to study participants, while allowing a quick data turn-around at Biostatistical Center. The main drawbacks to the NSC scannable forms are their ***per-unit cost*** and the necessity of purchasing ***proprietary hardware and software*** to read the forms. The goal in setting up the Teleform system was to attempt to apply the same technology to smaller treatment trials. Teleform permits the ***NSABP staff to design and read their own forms*** at a ***much reduced per-unit cost*** and does it all using ***generic PC hardware*** which can be simultaneously used for other research purposes. A secondary rationale for Teleform is that it has ***external fax entry capabilities*** which are not available through the NSC forms.

d. **Current Data Processing Procedures:** (See attached flow sheet.)

2. ASSESSMENT OF COMPONENTS

a. **Form Creation:** Three separate scannable forms were designed and created for C-06. The form creation time for the whole study was perhaps 100-120 hours, which includes numerous revisions from the QoL Committee. Subsequent form creation time should be much reduced. The form designer in Teleform operates as a simple word processor which also programs the data output at the same time the form is created. It is convenient and relatively flexible with a few minor irritating rigidities. It is capable of being used by secretary level staff who have some serious Windows based word processing experience. It has a flexible data output facility that will directly interface with many PC data bases.

b. **Foreign Language Forms:** French and Spanish language forms were created for C-06. Special accents are not readily available and were created by hand or borrowed from other character sets. One cut and paste (Spanish initial question mark) had to be done. The form designer



permits the form to be magnified several times which permits precise placement of accent marks. In short, foreign language scannable forms require extra work , but are quite "do-able."

c. **Form Printing:** The University of Pittsburgh printing office can create professional looking form that can be successfully read by the scanner. More important, they can also create left margin perforations that make page separation particularly easy and efficient. We recommend left margin perforation for all future scannable forms.

d. **Form Acceptance at Clinical Sites:** No objections have been raised to the design or use of scannable form during interactions with study coordinators from the sites. No negative feedback from patients so far.

e. **Scanning and Verification of Forms:** Scanning and verification speeds are largely dependent on hardware capabilities. ***Using the current hardware configuration, it takes approximately 3 minutes to fully process 1 page of data***. This time could be substantially reduced by increasing the clock speed of the CPU, the amount of RAM available for storage, and the processing speed of the scanner (see attached advertisment). The training required to carry out the scanning and verification tasks are minimal and could be done by staff at the level of work-study students or data entry clerks.

f. **Current Scanning Situation:** At the present time, a total of XXX C-06 forms have been scanned using the equipment in Dr. Day's office in A443 Crabtree Hall. The current procedure was set up as an interim means of monitoring the scanning process. It was planned that at some early point in the study, the scanning process would either be transferred out of Dr. Day's office to another location in NSABP or the scanning process would be dropped in favor of hand entry. The number of forms C-06 QoL forms being received is beginning to increase in a linear fashion and it is becoming increasing difficult to continue the scanning process with currently available hardware and staffing resources.

g. **Format and Quality of Data Output from Scanner:** Teleform is very flexible about the choice of data output formats. We are currently using comma delimited ASCII files. However, any type of delimited or undelimited ASCII file could be chose. In addition, Teleform will also create files formatted for specific data bases such as dBase, Access, Fox Pro, Oracle, etc. (but not 1032). Some small, unexpained quality problems have been noted by Ms. Goshal in the output files. A formal QA/QC has not been carried out on the NSABP data and probably should be done. QA/QC's carried out on other studies using Teleform in which Dr. Day is involved have shown error rates less than 1% for bubble entry data.

h. **Data Input to NSABP System:** Requires specialized input programming to 1032. However, not difficult or unreasonable.

3. ADDITIONAL UNTESTED TELEFORM COMPONENTS

a. **Direct Fax Data Entry:** Teleform includes the capacity for direct fax data entry from remote sites. An electronic image of the form is submitted for verification by Teleform. This facility may save time in the sites by making unnecessary form copying and submission.

b. **Intelligent Character Recognition (ICR):** We have avoided using ICR (numbers and alphabetical entries) for the C-06 study, but QA/QC on other studies has shown this component of Teleform to be reasonably reliable with a little training for the data entry people. It is a possible that ICR may be used with more complex forms in the future. No ICR is used in any of the NCS BCPT forms.

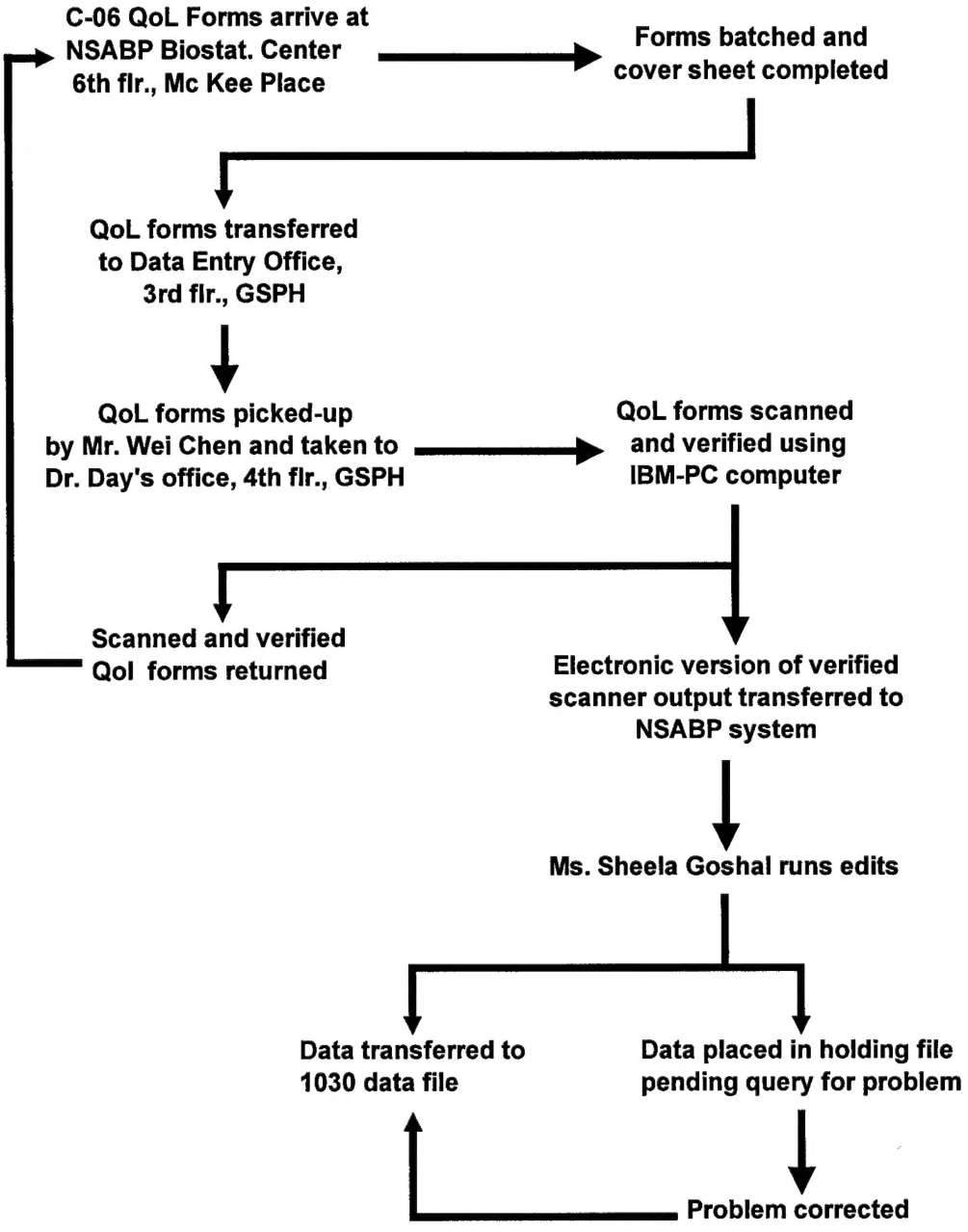
c. **Teleform Programming Language:** Teleform contains an extensive programming language that supports a number of additional functions beyond what is built into the Windows level software. This has not been tested in C-06.

4. COMPARISON WITH OTHER PRODUCTS

a. **NCS:** NCS is used in the BCPT and NSABP has extensive experience with this product. The currennt advantages of Teleform over NCS are local form design, per-unit cost, use of generic hardware, and direct fax entry. The current advantage of NCS over Teleform is speed of data scanning. Both systems appear to be equally reliable for bubble entry.

b. **Data Fax:** Insufficient experience is available with Data Fax to make an assessment. One source of experience with both systems is SWOG.

Flow Chart for Current Processing of C-06 Quality of Life Forms



first draft
24 Oct. 97